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(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; Plot No. 90, Sector - 32, Gurgaon, Haryana 122 001 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SATTIGERI, Viswajanani, J.** [IN/IN]; N-323, Vijayrattan Vihar, Gurgaon, Haryana 122001 (IN). **PALLE, Venkata, P.** [US/IN]; G 901 Sylvan Heights Sanewadi, Aundh, Pune (maharashtra) 411007 (IN). **SONI, Ajay** [IN/IN]; B-6, Om Vihar, Uttam Nagar, New Delhi 110059 (IN). **NAIK, Keshav, Prabhakar** [IN/IN]; c/o P.P. Naik, Inamdar Building, New Janata Colony, Gopalwadi Roady Daunf, Dist. Pune, Maharashtra 413801 (IN). **RAY, Abhijit** [IN/IN]; Sector C-1, 1408, Vasant Kunj, New Delhi 110070 (IN). **DASTIDAR, Sunanda, G.** [IN/IN]; B-138, Sarita Vihar, New Delhi 110044 (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

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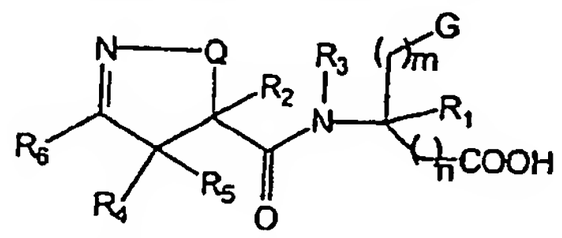
(54) Title: HETEROCYCLIC DERIVATIVES AS CELL ADHESION INHIBITORS



(I)

(57) **Abstract:** The present invention relates to certain heterocyclic derivatives of formula (I) , in particular isoxazoline and isothiazoline derivatives as cell adhesion inhibitors. The compounds of this invention can be useful, for inhibition and prevention of cell adhesion and cell adhesion mediated pathologies including inflammatory and autoimmune diseases such as bronchial asthma, rheumatoid arthritis, type I diabetes, multiple sclerosis, allograft rejection or psoriasis. This invention also relates to pharmacological compositions containing the compounds of the present invention, and methods of treating bronchial asthma, rheumatoid arthritis, multiple sclerosis, type I diabetes, psoriasis, allograft rejection, and other inflammatory and/or autoimmune disorders using the compounds.

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HETEROCYCLIC DERIVATIVES AS CELL ADHESION INHIBITORS

Field of the Invention

The present invention relates to certain heterocyclic derivatives, in particular isoxazoline and isothiazoline derivatives, as cell adhesion inhibitors. The compounds of this invention can be useful for inhibition and prevention of cell adhesion and cell adhesion mediated pathologies including inflammatory and autoimmune diseases, for example, bronchial asthma, rheumatoid arthritis, type I diabetes, multiple sclerosis, allograft rejection or psoriasis. This invention also relates to pharmacological compositions containing the compounds of the present invention, and methods of treating bronchial asthma, rheumatoid arthritis, multiple sclerosis, type I diabetes, psoriasis, allograft rejection, other inflammatory or autoimmune disorders using such compounds.

Background of the Invention

Cell adhesion is a process by which cells associate with each other, migrate towards a specific target or localize within the extra-cellular matrix. These interactions are mediated by specialized molecules called cell adhesion molecules (CAMs). CAMs have been demonstrated to participate in various cell-cell, cell-extracellular matrix, and platelet-platelet interactions. They influence the adhesion of leukocytes to the vascular endothelium, their transendothelial migration, retention at extravascular sites and activation of T cells and eosinophils. These processes are central to the pathogenesis of inflammatory and autoimmune diseases. Therefore, CAMs are considered as potential targets to treat such disorders.

CAMs can be classified into three groups - integrins, selectins and the immunoglobulin superfamily. Of these, integrins are key mediators in the adhesive interactions between hemopoietic cells and their microenvironment. They are comprised of alpha-beta heterodimers that integrate signals from outside to the inside of cells and vice versa. Integrins can be classified on the basis of the beta subunits they contain. For example, beta-1 subfamily contains beta-1 subunit noncovalently linked to one of the 10 different alpha subunits.

The alpha-4 beta-1 integrin, also known as VLA-4 (very late activation antigen 4), is a member of beta 1 integrin family and comprises of alpha-4 and beta-1 subunits. It

interacts with two specific ligands - the vascular cell adhesion molecule (VCAM-1) and the CS1 region of the protein fibronectin. Adhesion mediated by VLA-4 is central to the process of transendothelial migration of leukocytes. Ligation of VLA-4 is followed by gross rearrangement of the cytoskeleton leading to flattening of cells along the blood vessel wall followed by expression of specific molecules which digest the endothelial cell wall and diapedesis. Once in the extraluminal region, the interactions of VLA-4 with extracellular fibronectin play a crucial role in migration to the site of inflammation, T cell proliferation, expression of cytokines and inflammatory mediators. In addition, VLA-4 ligation provides co-stimulatory signals to the leukocytes, resulting in enhanced immunoreactivity. Therefore, it is expected that VLA-4 antagonists would ameliorate the immune response through twofold actions - inhibition of T cell recruitment at the site of inflammation and inhibition of costimulatory activation of immune cells.

Inhibitors of VLA-4 interactions have demonstrated beneficial therapeutic effects in several animal models of inflammatory, and allergic diseases including sheep allergic asthma (Abraham *et al.*, J. Clin. Invest., 93, 776 (1994)), arthritis (Wahl *et al.*, J. Clin. Invest. 94, 655 (1994)); experimental allergic encephomyelitis (Yednock *et al.*, Nature (Lond), 356, 63 (1992) and Baron *et al.*, J. Exp. Med., 177, 57 (1993)); contact hypersensitivity (Chisolm *et al.*, Eur J. Immunol., 23,682 (1993)); type I diabetes (Yang *et al.*, Proc. Natl. Acad. Sci. (USA), 90, 10494 (1993)) and inflammatory bowel disease (Podolsky *et al.*, J. Clin. Invest., 92, 372(1993)).

A region of CS1 moiety of fibronectin involved in the interaction with VLA-4 was identified as the tripeptide Leu-Asp-Val, also known as LDV (Komoriya *et al.*, J. Biol. Chem. 266, 15075(1991)). Taking a lead from this, several peptides containing the LDV sequence were synthesised which have shown to inhibit the *in vivo* interaction of VLA-4 to its ligands. (Ferguson *et al.*, Proc. Natl. Acad. Sci.(USA), 88, 8072 (1991); Wahl *et al.*, J. Clin. Invest., 94, 655(1994); Nowlin *et al.*, J. Biol. Chem., 268(27), 20352(1993) and PCT Application PCT/US 91/04862.

Despite these advances, there remains a need for inhibitors of VLA-4 dependent cell adhesion molecules. New generations of molecules with oral efficacy would provide useful agents for treatment, prevention or suppression of various inflammatory pathologies mediated by VLA-4 binding.

An article in *Ann. Rep. Med. Chem.*, 37, (2002) p. 65, summarizes the highlights of work in the area of VLA-4 biology and small molecule antagonists.

WO 98/53814 discloses heterocyclic amide compounds said to be useful as cell adhesion inhibitors. WO 98/58902 discloses molecules which are described as potent inhibitors of $\alpha_4\beta_1$ mediated adhesion to either VCAM or CS-1 and which can reportedly be used for treating or preventing $\alpha_4\beta_1$ adhesion mediated conditions. WO 99/20272 and U.S. Patent No. 6,069,163 disclose several azapeptide acids said to be useful as cell adhesion inhibitors. WO 99/06434 discloses 4-aminophenylalanine type compounds which apparently inhibit leukocyte adhesion mediated by VLA-4. WO 00/42054 and U.S. Patent No. 6,590,085 disclose several monosaccharide derivatives said to be useful as cell adhesion inhibitors. WO 00/43369 provides compounds which are said to bind to VLA-4. It also describes triazine derivatives which reportedly inhibit leukocyte adhesion mediated by VLA-4. WO 01/12183 describes heterocyclic amides said to be useful as cell adhesion inhibitors. WO 01/12186 discloses cell adhesion inhibitors which are said to interact with VLA-4 molecules, and thus inhibit VLA-4 dependent cell adhesion.

U.S. Patent No. 6,329,344 discloses several monosaccharide derivatives said to be useful as cell adhesion inhibitors. It generally relates to a group of substituted pentose and hexose monosaccharide derivatives which reportedly exhibit potent anti-cell adhesion and anti-inflammatory activities. U.S. Patent No. 6,291,511 discloses several biarylalkanoic acids said to be useful as cell adhesion inhibitors. U.S. Patent No. 6,020,347 discloses 4-substituted-4-piperidine carboxamide derivatives described as useful in the inhibition or prevention of cell adhesion and cell adhesion mediated pathologies. U.S. Patent No. 6,191,171 describes para-aminomethyl aryl carboxamide derivatives said to be useful as cell adhesion inhibitors. U.S. Patent No. 6,090,841 discloses substituted pyrrole derivatives said to be useful as cell adhesion inhibitors.

U.S. Patent No. 5,849,736 and WO 96/38426 disclose isoxazolines and isoxazoles which are described as useful antagonists of the platelets glycoprotein IIb/IIIa fibrinogen receptor complex or the vitronectin receptor. U.S. Patent No. 5,710,159 and WO 96/37492 disclose heterocyclic compounds including 3-[3-[3-(imidazolin-2-yl-amino)-propyloxy]-isoxazol-5-ylcarbonylamino]-2-(benzyloxycarbonylamino) -propionic acid, which are said to be useful as antagonists of the $\alpha_v\beta_3$ and related integrin receptors. U.S.

Patent No. 2004/0023900 discloses derivatives of monosaccharides said to be useful as cell adhesion inhibitors. U.S. Patent No. 2004/0029820 discloses derivatives of monosaccharides said to be useful as cell adhesion inhibitors.

GB 2354440 describes several aryl amides as cell adhesion inhibitors, and discloses compounds containing isoxazoline and isothiazoline moiety, which reportedly may be used as therapy for the inhibition, prevention and suppression of VLA-4 mediated cell adhesion and pathologies associated with that adhesion.

However, in view of the above, there remains a need for novel inhibitors of VLA-4 dependent cell adhesion molecules.

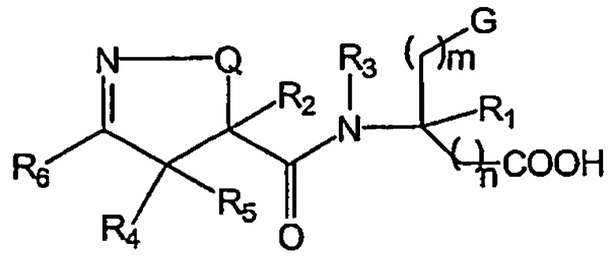
Summary of the Invention

The present invention provides substituted isoxazoline and isothiazoline derivatives, which can be used as cell adhesion inhibitors. Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides of these compounds are also provided.

Compounds provided herein were screened for inhibitory activity in a VLA-4 mediated cell adhesion assay and the classical murine hypersensitivity assay in mice. These compounds could be used in treatment of chronic, cell adhesion mediated, allergic, autoimmune and inflammatory disorders, such as bronchial asthma, multiple sclerosis, rheumatoid arthritis etc.

Pharmaceutical composition containing the compounds, and which may also contain pharmaceutically acceptable carriers or diluents, can be used for the treatment of cell adhesion mediated pathologies, including inflammatory and autoimmune diseases such as bronchial asthma, rheumatoid arthritis, type I diabetes, multiple sclerosis, allograft rejection or psoriasis.

In one aspect, provided are compounds having a structure of Formula I:



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides, wherein

m and **n** can be integers with the values 0, 1 or 2;

Q can be O or S;

$\mathbf{R_1}$ can be hydrogen or methyl;

$\mathbf{R_2}$ can be hydrogen or $(CH_2)_f(O)_gR_k$, wherein

f can be 0-6, g can be 0-1, and R_k can be C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or aryl;

$\mathbf{R_4}$ and $\mathbf{R_5}$ can independently be selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, heteroaryl, heterocyclyl, C_1-C_4 heteroarylalkyl and C_1-C_4 heterocyclylalkyl;

$\mathbf{R_6}$ can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl; and

$\mathbf{R_3}$ can be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, C_1-C_4 heteroarylalkyl or C_1-C_4 heterocyclylalkyl, and **G** can be aryl optionally substituted with one or more of X, $\equiv\!\!-(CH_2)_q-X$, heteroaryl substituted with one or more X or heterocyclyl substituted with one or more X; or when G is aryl, $\mathbf{R_3}$ and **G** together can optionally form a benzofused heterocyclic 5-6 membered ring along with the N to which R_3 is attached, wherein

q can be an integer 0-1 with the proviso that q cannot be 0 when X is a derivative of heteroatom, and

X can be hydrogen, alkyl, alkenyl, alkynyl, halogen, acyl, CF_3, nitro, carboxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl,

heterocyclylalkyl, $COOR_9$,-$(CH_2)_{0-4}$-O-R', –C(=O)NR_7R_8, $(CH_2)_{0-4}NR_7R_8$, $NHYR_9$ or -$NR_jC(=T)NR_dR_c$,

wherein

Y can be -C(=O), -C(=S) or SO_2;

R_d can be OH or R_c;

T can be O, S, -N(CN), -N(NO_2) or -CH(NO_2);

R_9 can be alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

R' can be hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryl, acyl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl or C(=O)NR_tR_c;

R_7 and R_8 can each independently be hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl, or R_7 and R_8 can together join to form a 5-8 membered-ring containing 0-4 heteroatoms selected from O, S and N, wherein the ring can be optionally benzofused and optionally substituted with one or more of alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, carboxy, alkoxy, aryloxy, acyl, aryl, amino, substituted amino, oxo, CF_3, halogen, cycloalkylalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or OC(=O)NR_tR_c;

R_t and R_c can each independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or SO_2R_9; and

R_j can be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, C_1-C_6 aralkyl, C_1-C_6 heteroarylalkyl or C_1-C_6 heterocyclylalkyl, wherein

R_j and R_c optionally can together be a part of a 5- or 6-membered ring along with the N atom to which they are attached,

with the provisos that:

a) when n is 1 and Q is O, then R_6 cannot be substituted with amino, substituted amino, $Z(CH_2)_pR_w$ or ZR_v,

wherein Z is O or $S(O)_q$, q and p is an integer 0-2, R_w is amino, substituted amino and R_v is cycloalkyl, cycloalkylalkyl, heterocyclyl or heterocyclylalkyl;

b) when Q is O, then R_6 cannot be a 5-membered N-containing heteroaryl having one or more heteroatoms selected from S, O or N, or C=O or SO_2 group in the ring; or

R_6 cannot be a 5-membered N containing heteroaryl having substituted or unsubstituted amino groups; and one or more of S, O, N, C=O or SO_2 in the heteroaryl ring; and

c) when Q is O, then R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring; or

R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring and substituted or unsubstituted amino groups, and the point of attachment of the heteroaryl is from the carbon atom adjacent to N atom.

The compounds can include one or more of the following embodiments. For example, Q can be O. In another embodiment, R_6 can be alkyl, aryl, cycloalkyl, aralkyl, heterocyclyl or heteroaryl. In another embodiment, R_6 can optionally be substituted alkyl, optionally substituted aryl, optionally substituted aralkyl. R_6 can be phenyl, chlorophenyl, fluorophenyl, dichlorophenyl, methoxyphenyl, dimethoxyphenyl, tolyl, tert-butyl, methylphenylethyl, cyclohexyl, thiophenyl, pyridinyl, quinolinyl or naphthalenyl.

In another embodiment, R_4 and R_5 can each be hydrogen. In yet another embodiment, R_3 can be alkyl or hydrogen. In another embodiment, R_2 can be an alkyl (*e.g.*, methyl) or hydrogen. R_1 can be hydrogen. G can optionally be substituted aryl, *e.g.*, phenyl, dichloro-benzoylamino-phenyl, dichloro-benzyloxyphenyl or dimethoxybiphenyl.

In another aspect, provided are compounds selected from:

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 1),

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 2),

(S)-3-(2′,6′-Dimethoxy-biphenyl-4-yl)-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 3),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-phenethyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 4),

(S)-2-{[3-(3-Chloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 5),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2-fluoro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 6),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2,6-dimethoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 7),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino}-propionic acid (Compound No. 8),

(S)-2-{[3-(2-Chloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 9),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2,6-dichloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 10),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[5-methyl-3-(1-phenyl-ethyl)-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 11),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 12),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(3,4-dimethoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino]-propionic acid (Compound No. 13),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-p-tolyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 14),

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[(3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 15),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-quinolin-8-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 16),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-thiophen-2-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 17),

(S)-[(5-Methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-phenyl-acetic acid (Compound No. 18),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-quinolin-5-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 19),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-quinolin-5-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 20),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-pyridin-3-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 21),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-pyridin-3-yl-4,5-dihydro-isoxazle-5-carbonyl)-amino]-propionic acid (Compound No. 22),

(S)-2-[(3-Cyclohexyl-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 23),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-naphthalen-2-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 24),

(S)-2-[(3-tert-Butyl-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 25),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(3,5-dimethyl-4,5-dihydro-isoxazole-5-carbonyl}-amino]-propionic acid (Compound No. 26), and

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides or polymorphs.

In yet another aspect, provided are pharmaceutical compositions comprising a therapeutically effective amount of a compound provided herein.

together with one or more pharmaceutically acceptable carriers, excipients or diluents.

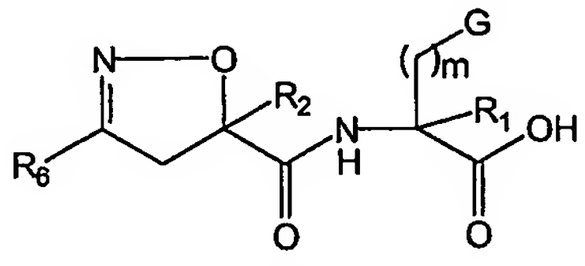
In another aspect, provided are methods of treating an animal or a human suffering from bronchial asthma, rheumatoid arthritis, type I diabetes, multiple sclerosis, psoriasis, allograft rejection or other inflammation and/or autoimmune disorders comprising administering to said animal or human a therapeutically effective amount of a compound provided herein.

In another aspect, provided are methods of preventing, inhibiting or suppressing cell adhesion in an animal or human comprising administering to said animal or human a therapeutically effective amount of a compound provided herein.

In another aspect, provided are methods of treating an animal or a human suffering from bronchial asthma, rheumatoid arthritis, type I diabetes, multiple sclerosis, psoriasis, allograft rejection or other inflammation and/or autoimmune disorders comprising administering to said animal or human a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein together with one or more pharmaceutically acceptable carriers, excipients or diluents.

In another aspect, provided are methods of preventing, inhibiting or suppressing cell adhesion in an animal or human comprising administering to said animal or human a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein together with one or more pharmaceutically acceptable carriers, excipients or diluents.

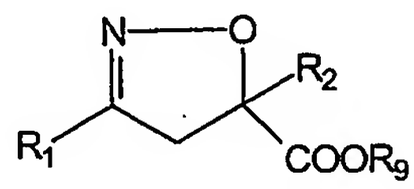
In yet another aspect, provided are processes for preparing a compound of Formula IX



Formula IX

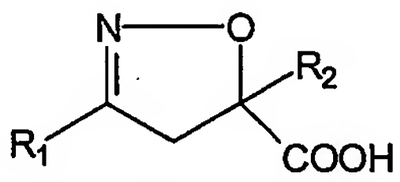
comprising the steps of:

a) hydrolyzing a compound of Formula V



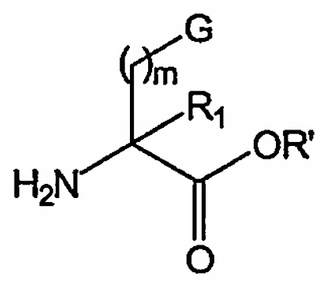
Formula V

to form a compound of Formula VI;



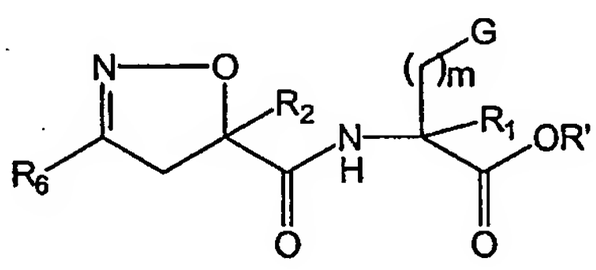
Formula VI

b) reacting the compound of Formula VI with a compound of Formula VII



Formula VII

to form a compound of Formula VIII; and



Formula VIII

c) hydrolyzing the compound of Formula VIII to yield a compound of Formula IX,

wherein

m can be an integer with a value of 0, 1 or 2;

$\mathbf{R_1}$ can be hydrogen or methyl;

$\mathbf{R_2}$ can be hydrogen or $(CH_2)_f(O)_gR_k$, wherein

f can be 0-6, g can be 0-1, and R_k can be C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or aryl;

R_6 can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl; and

G can be aryl optionally substituted with one or more of X, $\equiv\!\!-(CH_2)_q-X$, heteroaryl substituted with one or more X or heterocyclyl substituted with one or more X, wherein

q can be an integer 0-1 with the proviso that q cannot be 0 when X is a derivative of heteroatom, and

X can be hydrogen, alkyl, alkenyl, alkynyl, halogen, acyl, CF_3, nitro, carboxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, $COOR_9$,-$(CH_2)_{0-4}$-O-R′, –C(=O)NR_7R_8, $(CH_2)_{0-4}NR_7R_8$, $NHYR_9$ or -$NR_jC(=T)NR_dR_c$,

wherein

Y can be -C(=O), -C(=S) or SO_2;

R_d can be OH or R_c;

T can be O, S, -N(CN), -N(NO_2) or -CH(NO_2);

R_9 can be alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

R′ can be hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryl, acyl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl or C(=O)NR_tR_c;

R_7 and R_8 each can independently be hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl, or R_7 and R_8 can together join to form a 5-8 membered-ring containing 0-4 heteroatoms selected from O, S and N, wherein the ring can be optionally benzofused and optionally substituted with one or more of alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, carboxy, alkoxy, aryloxy,

acyl, aryl, amino, substituted amino, oxo, CF_3, halogen, cycloalkylalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or $OC(=O)NR_tR_c$;

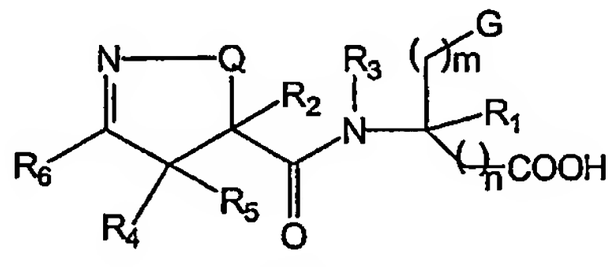
R_t and R_c each can independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or SO_2R_9; and

R_j can be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, C_1-C_6 aralkyl, C_1-C_6 heteroarylalkyl or C_1-C_6 heterocyclylalkyl, wherein

R_j and R_c optionally can together be a part of a 5- or 6-membered ring along with the N atom to which they are attached.

Detailed Description of the Invention

In accordance with one aspect of the invention, there are provided compounds having a structure of Formula I:



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides, wherein

m and **n** can be integers with the values 0, 1 or 2;

Q can be O or S;

$\mathbf{R_1}$ can be hydrogen or methyl;

$\mathbf{R_2}$ can be hydrogen or $(CH_2)_f(O)_gR_k$, wherein

f can be 0-6, g can be 0-1, and R_k can be C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or aryl;

$\mathbf{R_3}$ can be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, C_1-C_4 heteroarylalkyl or C_1-C_4 heterocyclylalkyl;

$\mathbf{R_4}$ and $\mathbf{R_5}$ can be independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, heteroaryl, heterocyclyl, C_1-C_4 heteroarylalkyl and C_1-C_4 heterocyclylalkyl;

$\mathbf{R_6}$ can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl; and

G can be aryl optionally substituted with one or more of X, $\equiv\!\!-(CH_2)_q-X$, heteroaryl substituted with one or more X or heterocyclyl substituted with one or more X, wherein

when G is aryl, $\mathbf{R_3}$ and **G** may also together form a benzofused heterocyclic 5-6 membered ring along with the N to which R_3 is attached;

q can be an integer 0-1 with the proviso that q cannot be 0 when X is a derivative of heteroatom, and

X can be hydrogen, alkyl, alkenyl, alkynyl, halogen, acyl, CF_3, nitro, carboxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, $COOR_9$,-$(CH_2)_{0-4}$-O-R′, –C(=O)NR_7R_8, $(CH_2)_{0-4}NR_7R_8$, $NHYR_9$ or -$NR_jC(=T)NR_dR_c$,

wherein

Y can be -C(=O), -C(=S) or SO_2;

R_d can be OH or R_c;

T can be O, S, -N(CN), -N(NO_2) or -CH(NO_2);

R_9 can be alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl);

R′ can be hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryl, acyl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl or C(=O)NR_tR_c);

R_7 and R_8 can independently be hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl, or R_7 and R_8 may together join to form a 5-8 membered-ring containing 0-4 heteroatoms selected from O, S and N, wherein the ring may be optionally benzofused and optionally substituted with one or more of alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, carboxy, alkoxy, aryloxy, acyl, aryl, amino, substituted amino, oxo, CF_3, halogen, cycloalkylalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or $OC(=O)NR_tR_c$);

R_t and R_c may independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or SO_2R_9); and

R_j can be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, C_1-C_6 aralkyl, C_1-C_6 heteroarylalkyl or C_1-C_6 heterocyclylalkyl), wherein

R_j and R_c can also be together a part of a 5- or 6-membered ring along with the N atom to which they are attached,

with the provisos that:

1) when n=1 and Q is O, then R_6 cannot be substituted with amino, substituted amino, $Z(CH_2)_pR_w$ or ZR_v,

wherein Z is O or $S(O)_q$, q and p is an integer 0-2, R_w is amino, substituted amino and R_v is cycloalkyl, cycloalkylalkyl, heterocyclyl or heterocyclylalkyl;

2) when Q is O, then R_6 cannot be a 5-membered N-containing heteroaryl having one or more heteroatoms selected from S, O or N, or C=O or SO_2 group in the ring; or

R_6 cannot be a 5-membered N containing heteroaryl having substituted or unsubstituted amino groups; and one or more of S, O, N, C=O or SO_2 in the heteroaryl ring; and

3) when Q is O, then R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring; or

R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring and substituted or unsubstituted amino groups, and the point of attachment of the heteroaryl is from the carbon atom adjacent to N atom.

The following definitions apply to terms as used herein:

The term "alkyl," unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term can be exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl groups may be substituted further with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, aryl, heterocyclyl, heteroaryl, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, $-NHC(=O)R_f$, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-NHC(=O)NR_fR_q$, -C(=O)heteroaryl, C(=O)heterocyclyl, $-O-C(=O)NR_fR_q$ {wherein R_f and R_q are independently selected from alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl}, nitro, or $-SO_2R_{60}$ (wherein R_{60} is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, carboxy, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-OC(=O)NR_fR_q$, $-NHC(=O)NR_fR_q$ (wherein R_f and R_q are the same as defined earlier), hydroxy, alkoxy, halogen, CF_3, cyano, and $-SO_2R_{60}$, (wherein R_{60} are the same as defined earlier); or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or $-NR_a-$ {wherein R_a is selected from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl,$-C(=O)OR_f$ (wherein R_f is the same as defined earlier), SO_2R_{60} (where R_{60} is as defined earlier), or $-C(=O)NR_fR_q$ (wherein R_f and R_q are as defined earlier)}. Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, carboxy, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-O-C(=O)NR_fR_q$ (wherein R_f and R_q are the same as defined earlier) hydroxy, alkoxy, halogen, CF_3, cyano,

and $-SO_2R_{60}$ (where R_{60} is same as defined earlier); or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "alkenyl," unless otherwise specified, refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group having from 2 to 20 carbon atoms with cis, trans, or geminal geometry. In the event that alkenyl is attached to a heteroatom, the double bond cannot be alpha to the heteroatom. Alkenyl groups may be substituted further with one or more substituents selected from alkyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, -NHC (=O)R_f, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroaryl alkyl, aminosulfonyl, aminocarbonylamino, alkoxyamino, nitro, or SO_2R_{60} (wherein R_{60} is same as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, -CF_3, cyano, -NR_fR_q, -C(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier) and -SO_2R_{60} (where R_{60} is same as defined earlier).

The term "alkynyl," unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, having from 2 to 20 carbon atoms. In the event that alkynyl is attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. Alkynyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, -NHC(=O)R_f, -NR_fR_q, -NHC(=O)NR_fR_q, -C(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), or -SO_2R_{60} (wherein R_{60} is as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3, -NR_fR_q, -C(=O)NR_fR_q,

-NHC(=O)NR_fR_q, -C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), cyano, or –SO_2R_{60} (where R_{60} is same as defined earlier).

The term "cycloalkyl," unless otherwise specified, refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless otherwise constrained by the definition. Such cycloalkyl groups can include, for example, single ring structures, including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring structures, including adamantanyl, and bicyclo [2.2.1] heptane, or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like. Spiro and fused ring structures can also be included. Cycloalkyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, -NR_fR_q, -NHC (=O) NR_fR_q, -NHC (=O) R_f, -C (=O) NR_fR_q, -O-C (=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, or SO_2-R_{60} (wherein R_{60} is same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, CF_3, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -OC(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), cyano or –SO_2R_{60} (where R_{60} is same as defined earlier). "Cycloalkylalkyl" refers to alkyl-cycloalkyl group linked through alkyl portion, wherein the alkyl and cycloalkyl are the same as defined earlier.

The term "alkoxy" denotes the group O-alkyl, wherein alkyl is the same as defined above.

The term "aryl," unless otherwise specified, refers to carbocyclic aromatic groups, for example, phenyl, biphenyl or naphthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF_3, cyano, nitro, $COOR_e$ (wherein R_e is hydrogen, alkyl, alkenyl, cycloalkyl, aralkyl, heterocyclylalkyl, heteroarylalkyl), NHC(=O)R_f, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), -SO_2R_{60} (wherein R_{60} is same as defined earlier), carboxy,

heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino. The aryl group optionally may be fused with a cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S.

The term "aralkyl," unless otherwise specified, refers to alkyl-aryl linked through an alkyl portion (wherein alkyl is as defined above) and the alkyl portion contains 1-6 carbon atoms and aryl is as defined below. Examples of aralkyl groups include benzyl, ethylphenyl and the like.

The term "aralkenyl," unless otherwise specified, refers to alkenyl-aryl linked through alkenyl (wherein alkenyl is as defined above) portion and the alkenyl portion contains 1 to 6 carbon atoms and aryl is as defined below.

The term "aryloxy" denotes the group O-aryl, wherein aryl is as defined above.

The term "carboxy," as defined herein, refers to –C(=O)OH.

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having from 8 to 10 ring atoms, with one or more heteroatom(s) independently selected from N, O or S optionally substituted with 1 to 4 substituent(s) selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, heteroaryl, $-NR_fR_q$, CH=NOH, $-(CH_2)_wC(=O)R_g$ {wherein w is an integer from 0-4 and R_g is hydrogen, hydroxy, OR_f, NR_fR_q, $-NHOR_z$ or –NHOH}, $-C(=O)NR_fR_q$ and $-NHC(=O)NR_fR_q$, $-SO_2R_{60}$, $-O-C(=O)NR_fR_q$, $-O-C(=O)R_f$, $-O-C(=O)OR_f$ (wherein R_{60}, R_f and R_q are as defined earlier, and R_z is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, the substituents are attached to a ring atom, *i.e.*, carbon or heteroatom in the ring. Examples of heteroaryl groups include oxazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, or benzoxazolyl, and the like.

The term 'heterocyclyl," unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 4 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and optionally are

benzofused or fused heteroaryl having 5-6 ring members and/or optionally are substituted, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, heterocyclyl, heteroaryl, -O-C(=O)R_f, -O-C(=O)OR_f, -C(=O)NR_fR_q, SO_2R_{60}, -O-C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -NR_fR_q (wherein R_{60}, R_f and R_q are as defined earlier) or guanidine. Heterocyclyl can optionally include rings having one or more double bonds. Unless otherwise constrained by the definition, the substituents are attached to the ring atom, *i.e.*, carbon or heteroatom in the ring. Also, unless otherwise constrained by the definition, the heterocyclyl ring optionally may contain one or more olefinic bond(s). Examples of heterocyclyl groups include oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl or piperazinyl.

"Heteroarylalkyl" refers to alkyl-heteroaryl group linked through alkyl portion, wherein the alkyl and heteroaryl are as defined earlier.

"Heterocyclylalkyl" refers to alkyl-heterocyclyl group linked through alkyl portion, wherein the alkyl and heterocyclyl are as defined earlier.

"Acyl" refers to –C(=O)R″ wherein R″ is selected from hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Alkylcarbonyl" refers to –C(=O)R″, wherein R″ is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Alkylcarboxy" refers to –O–C(=O)R″, wherein R″ is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Amine," unless otherwise specified, refers to $–NH_2$. "Substituted amine," unless otherwise specified, refers to –N $(R_k)_2$, wherein each R_k independently is selected from hydrogen {provided that both R_k groups are not hydrogen (defined as "amino")}, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, acyl, SO_2R_{60} (wherein R_{60} is as defined above), -C(=O)NR_fR_q, NHC(=O)NR_fR_q, or -NHC(=O)OR_f (wherein R_f and R_q are as defined earlier).

"Thiocarbonyl" refers to –C(=S)H. "Substituted thiocarbonyl" refers to–C(=S)R″, wherein R″ is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,

heteroarylalkyl or heterocyclylalkyl, amine or substituted amine.

Unless otherwise constrained by the definition, all substituents optionally may be substituted further by 1-3 substituents selected from alkyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3, cyano, $-C(=T)NR_fR_q$, $-O(C=O)NR_fR_q$ (wherein R_f, R_q and T are the same as defined earlier) and $-OC(=T)NR_fR_{q,}$, $-SO_2R_{60}$ (where R_{60} is the same as defined earlier).

The term "leaving group" refers to groups that exhibit or potentially exhibit the properties of being labile under the synthetic conditions and also, of being readily separated from synthetic products under defined conditions. Examples of leaving groups include, but are not limited to, halogen (*e.g.*, F, Cl, Br, I), triflates, tosylate, mesylates, alkoxy, thioalkoxy, or hydroxy radicals and the like.

The term "activated derivative of a carboxylic acid", for example, that of a suitable protected amino acid, aliphatic acid or an aromatic acid refer to the corresponding acyl halide (e.g. acid fluoride, acid chloride and acid bromide), corresponding activated esters (e.g. nitro phenyl ester, the ester of 1- hydroxybenzotriazole or the ester of hydroxysuccinimide, HOSu) or a mixed anhydride for example anhydride with ethyl chloroformate and other conventional derivatives within the skill of the art.

The term "protecting groups" refers to moieties that prevent chemical reaction at a location of a molecule intended to be left unaffected during chemical modification of such molecule. Unless otherwise specified, protecting groups may be used on groups, such as hydroxy, amino, or carboxy. Examples of protecting groups are found in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd Ed., John Wiley and Sons, New York, N.Y., which is incorporated herein by reference. The species of the carboxylic protecting groups, amino protecting groups or hydroxy protecting groups employed are not critical, as long as the derivatised moieties/moiety is/are stable to conditions of subsequent reactions and can be removed without disrupting the remainder of the molecule.

The term "pharmaceutically acceptable salts" refers to derivatives of compounds that can be modified by forming their corresponding acid or base salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acids

salts of basic residues (such as amines), or alkali or organic salts of acidic residues (such as carboxylic acids), and the like.

"Amino acid" refers to both natural and unnatural amino acids. The term "natural amino acids," as used herein, represents the twenty-two naturally-occurring amino acids glycine, alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagines, glutamic acid, glutamine, γ-carboxyglutamic acid, arginine, ornithine and lysine in their L form. The term "unnatural amino acid," as used herein, represents the 'D' form of the twenty-two naturally-occurring amino acids described above. It is further understood that the term "unnatural amino acids" includes homologues of the natural amino acids, and synthetically modified forms of the natural amino acids, such as those commonly utilized in the peptide chemistry arts when preparing synthetic analogues of naturally occurring peptides, including D and L forms. The synthetically modified forms include amino acids having alkylene chains shortened or lengthened by up to two carbon atoms, amino acids comprising optionally substituted aryl groups, and amino acids comprised halogenated groups preferably halogenated alkyl and aryl groups. The term "unnatural amino acids" as used herein also represents beta amino acids.

The term "peptide" refers to a molecule comprising a series of amino acids linked through amide linkages. Dipeptides comprise 2 amino acids, tripeptides comprise 3 amino acids and tetrapeptides comprise four amino acids, wherein the term amino acid is as defined earlier.

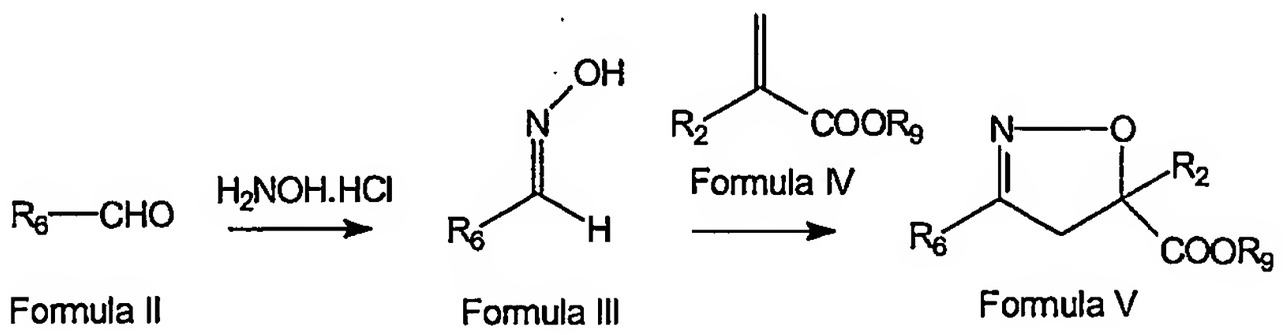
The present disclosure includes all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

The compounds provided herein can contain one or more asymmetric carbon atoms and may thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although specific compounds may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at

any given chiral center or mixtures thereof are envisioned as part of the invention. Although amino acids and amino acid side chains may be depicted in a particular configuration, both natural and unnatural forms are envisioned.

The compounds disclosed herein may be prepared by techniques well known in the art and familiar to the skilled synthetic organic chemist. (The intermediates were prepared following, for example, *J. Org. Chem.*, (2002), 67, 876-882; *Tetrahedron*, (1983), 39(13), 2227-2230; *J.Org.Chem.*, (1998), 63(18), 6319-6328; *J.Med.Chem.*, (1999), 42, 2752-2759; *J.Med.Chem.*, (1998), 41, 266-270; *J.Comb.Chem.*, (2002), 4, 652-655). In addition, the compounds provided herein may be prepared by, for example, the following reaction sequences, for example as depicted in Schemes I, II, III and IV.

Scheme I



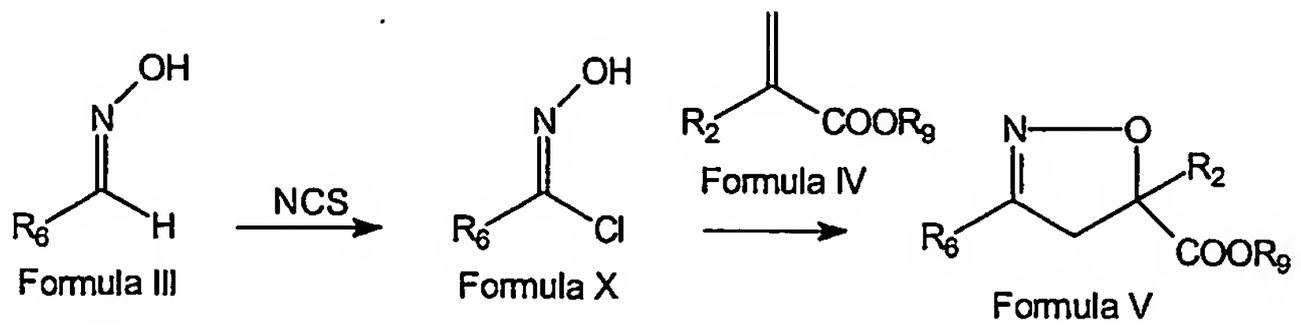
Compounds of Formula V can be prepared following Scheme I. Thus, compounds of Formula II can be reacted with hydroxylamine HCl to form compounds of Formula III (wherein R_6 is same as defined earlier). Compounds of Formula III can be reacted with compounds of Formula IV (wherein R_9, R_2 is same as defined earlier) to form compounds of Formula V.

Compounds of Formula II can be reacted with hydroxylamine hydrochloride to form compounds of Formula III in presence of one or more salts, for example, acetate salts, *e.g.*, sodium acetate, potassium acetate or mixtures thereof. The reaction can also be carried out in one or more organic solvents, for example, an alcoholic solvent, *e.g.*, ethanol, methanol, propanol, or mixtures thereof.

Compounds of Formula III can be reacted with compounds of Formula IV to form compounds of Formula V in presence of one or more oxidizing agents, for example, sodium hypochlorite, calcium hypochlorite or mixtures thereof. The reaction can also be carried out in one or more organic solvents, for example, tetrahydrofuran,

dichloromethane, dimethylformamide, acetonitrile or mixtures thereof. Further, the reaction can be carried out in the presence of one or more amines, for example, triethylamine, pyridine or mixture thereof, to accelerate the reaction process.

Scheme II

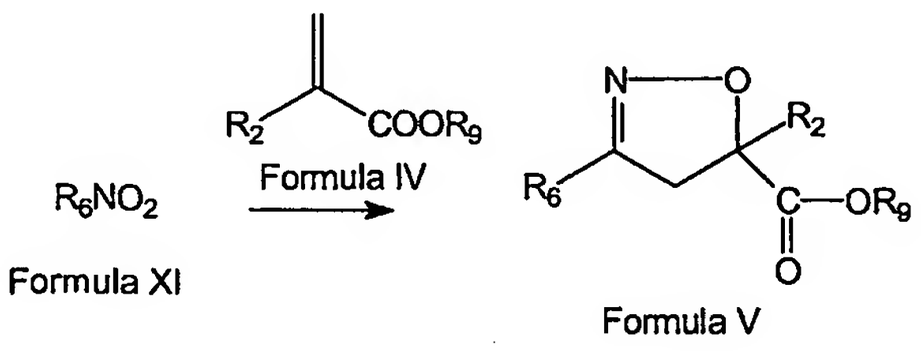


Compounds of Formula V can be prepared, for example, following Scheme II. Thus compounds of Formula III can be reacted with N-chlorosuccinimide (NCS) to form compounds of Formula X. Compounds of Formula X can be reacted with compounds of Formula IV to form compounds of Formula V.

Compounds of Formula III can be reacted with N-chlorosuccinimide to yield compounds of Formula X in one or more organic solvents, for example, non-protic solvents, *e.g.*, dimethylformamide, tetrahydrofuran or mixtures thereof. N-bromosuccinimide can be used instead of N-chlorosuccinimide to form compounds of Formula X having Br instead of Cl.

Compounds of Formula X can be reacted with compounds of Formula IV to form compounds of Formula V in presence of one or more organic bases, for example, triethylamine, diisopropylethylamine, pyridine or mixtures thereof. The reaction can also be carried out in one or more organic solvents, for example, tetrahydrofuran, dimethylformamide, dioxane or mixtures thereof.

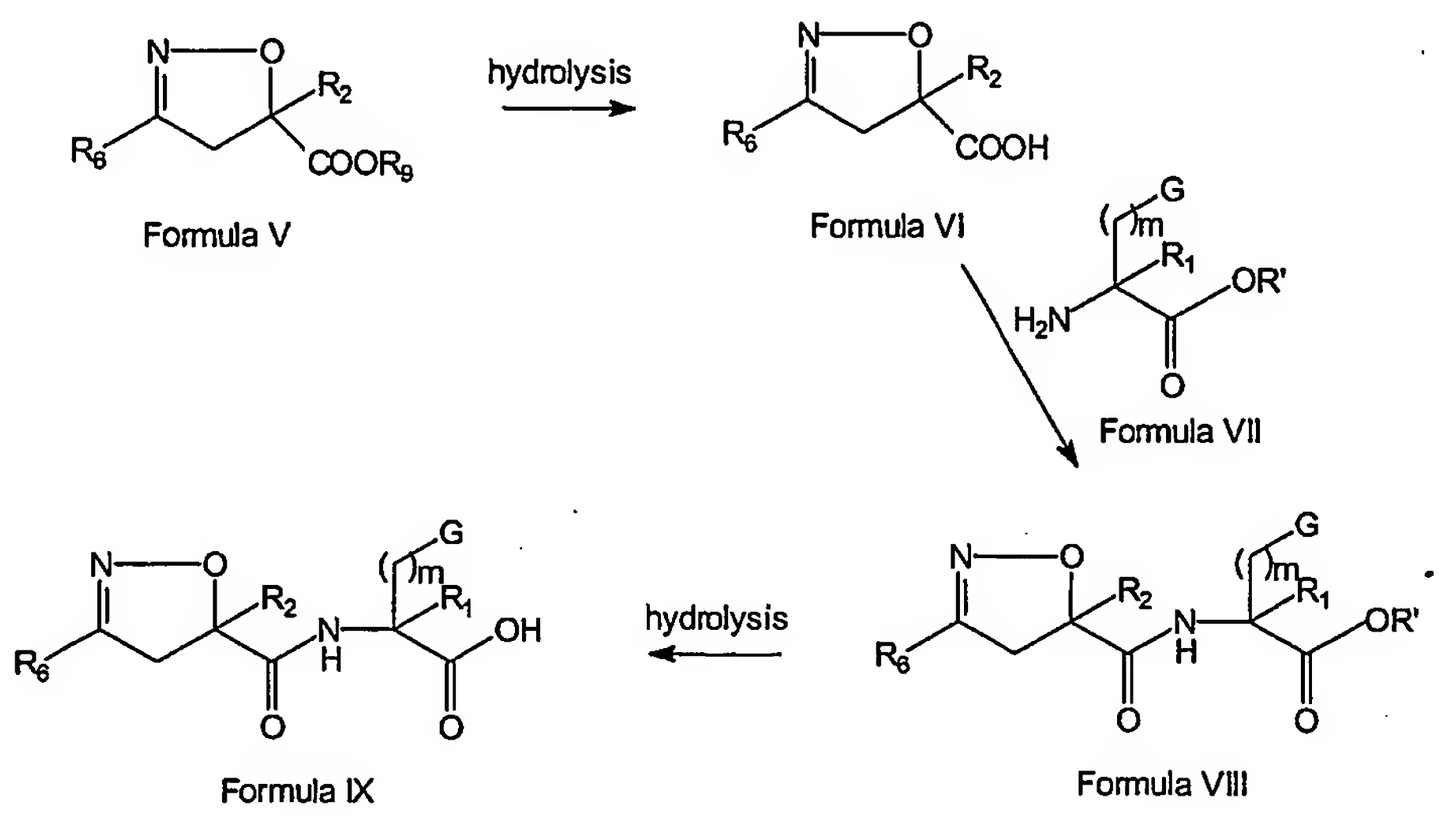
Scheme III



Compounds of Formula V can be prepared, for example, following Scheme III. Thus compounds of Formula XI (wherein R_6 is same as defined earlier) can be reacted with compounds of Formula IV to form compounds of Formula V.

Compounds of Formula XI can be reacted with compounds of Formula IV to form compounds of Formula V with one or more condensing agents, for example, trimethylsilyl chloride, and catalytic amounts of one or more acids, for example, *p*-toluenesulphonic acid. The reaction can also be carried out in presence of one or more bases, for example, triethylamine, diisopropylethyl amine, pyridine or mixtures thereof. The reaction can also be carried out in the presence of one or more solvents, for example, benzene, acetonitrile or mixtures thereof.

Scheme IV



Compounds of Formula IX can be prepared, for example, following Scheme IV. Thus compounds of Formula V (from, for example, any of Schemes I, II or III, or from other methods) can be hydrolyzed to form compounds of Formula VI. Compounds of Formula VI can be reacted with compounds of Formula VII to form compounds of Formula VIII. Compounds of Formula VIII can undergo ester saponification to form compounds of Formula IX (wherein R_1, R_2, R_6, R', G and m are same as defined earlier).

Compounds of Formula V can be hydrolyzed to form compounds of Formula VI in the presence of one or more bases, for example, lithium hydroxide, sodium hydroxide,

potassium hydroxide or mixtures thereof. The reaction can also be carried out in one or more solvents, for example, aqueous tetrahydrofuran, aqueous methanol, aqueous ethanol or mixtures thereof.

Compounds of Formula VI can be reacted with compounds of Formula VII to form compounds of Formula VIII with one or more condensing agents, for example, 1-(3-dimethylamino propyl)-3-ethyl-carbodimide, dicyclohexylcarbodiimide or mixtures thereof. The reaction can also be carried out in the presence of 1-hydroxbenzotriazole, and one or more bases, for example, N-methylmorpholine, triethylamine or mixtures thereof. The reaction can also be carried out in one or more solvents, for example, dimethylformamide, tetrahydrofuran, or mixtures thereof.

Compounds of Formula VIII can be saponified to form compounds of Formula IX in presence of one or more bases, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide or mixtures thereof. The reaction can also be carried out in the presence of one or more solvents, for example, aqueous tetrahydrofuran, aqueous methanol, aqueous ethanol or mixtures thereof,

Illustrative compounds prepared following Scheme I followed by Scheme IV include, for example:

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 1);

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 2);

(S)-3-(2′,6′-Dimethoxy-biphenyl-4-yl)-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 3);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-phenethyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 4);

(S)-2-{[3-(3-Chloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 5);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2-fluoro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 6);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2,6-dimethoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 7);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino}-propionic acid. (Compound No. 8);

(S)-2-{[3-(2-Chloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 9);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2,6-dichloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 10);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[5-methyl-3-(1-phenyl-ethyl)-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid. (Compound No. 11);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 12);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(3,4-dimethoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino]-propionic acid (Compound No. 13);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-p-tolyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 14);

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[(3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 15);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-quinolin-8-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 16);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-thiophen-2-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 17);

(S)-[(5-Methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-phenyl-acetic acid. (Compound No. 18);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[((5S)-5-methyl-3-quinolin-5-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid. (Compound No. 19);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[((5R)-5-methyl-3-quinolin-5-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid. (Compound No. 20);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[((5S)-5-methyl-3-pyridin-3-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid. (Compound No. 21); and

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[((5R)-5-methyl-3-pyridin-3-yl-4,5-dihydro-isoxazle-5-carbonyl)-amino]-propionic acid. (Compound No. 22).

Illustrative compounds prepared following Scheme II followed by Scheme IV include, for example:

(S)-2-[(3-Cyclohexyl-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 23);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-naphthalen-2-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid. (Compound No. 24); and

(S)-2-[(3-tert-Butyl-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 25).

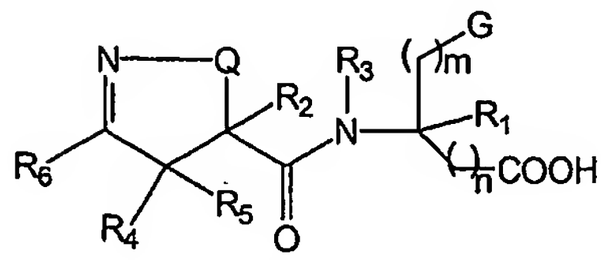
Illustrative compounds prepared following Scheme III followed by Scheme IV include, for example:

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(3,5-dimethyl-4,5-dihydro-isoxazole-5-carbonyl}-amino]-propionic acid. (Compound No. 26).

Pharmaceutically acceptable salts of the acids of Formula I can be prepared with an appropriate amount of one or more bases, for example, alkali or alkaline earth metal hydroxides, *e.g.*, sodium, potassium, lithium, calcium or magnesium, or one or more organic bases, for example, amines, *e.g.*, dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzyl amine and the like; or quaternary ammonium hydroxides, *e.g.*, tetramethylammonium hydroxide and the like; or mixtures thereof.

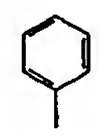
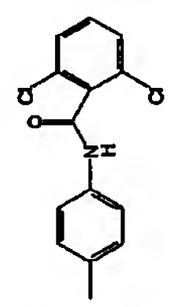
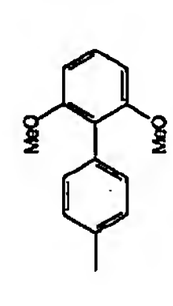
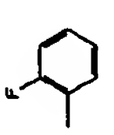
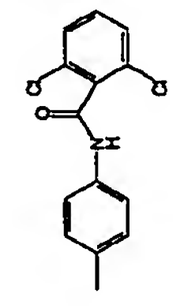
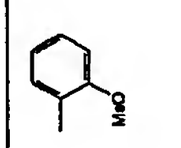
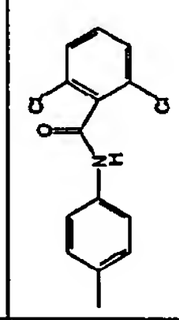
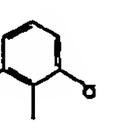
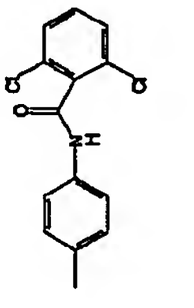
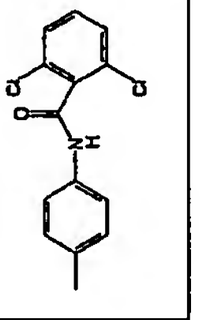
Illustrative compounds provided herein produced by Schemes I-IV are listed below in Table I.

TABLE I



Formula I

wherein R_1,R_3, R_4, R_5 are hydrogen, Q is O, and n=0.

Compound No.	m	R_6	R_2	G
1	1		CH_3	
3.	1		CH_3	
5.	1		CH_3	
7.	1		CH_3	
9.	1		CH_3	
11.	1		CH_3	
2	1		CH_3	
4.	1		CH_3	
6.	1		CH_3	
8.	1		CH_3	
10.	1		CH_3	
12	1		H	

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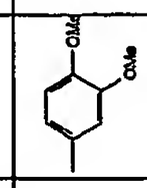
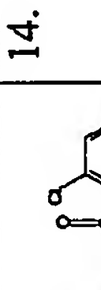
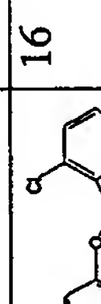
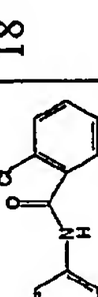
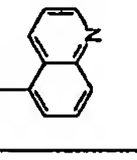
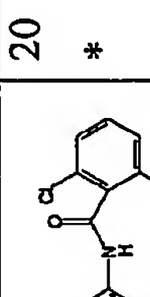
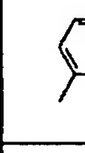
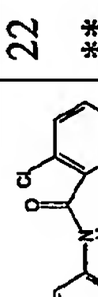
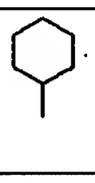
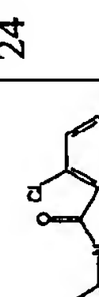
Compound No.	m	R_6	R_2	G
13.	1		CH_3	—
14.	1		CH_3	
15.	1		H	—
16	1		CH_3	
17.	1		CH_3	—
18	0		CH_3	
19	1		CH_3	—
20 *	1		CH_3	
21	1		CH_3	—
22 **	1		CH_3	
23	1		CH_3	—
24	1		CH_3	

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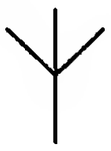
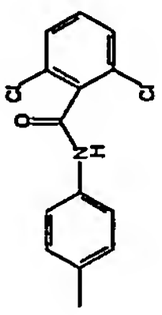
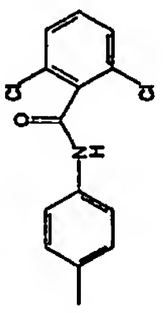
RLL-501WQ

Compound No.	m	R_6	R_2
25	1		CH_3

*represents diastereomer of compound 19

**represents diastereomer of compound 21

G	Compound No.	m	R_6	R_2
	26.	1	$-CH_3$	CH_3
				

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

Examples

Example 1 - Scheme I and IV: Synthesis of (S)-3-[4-(2,6-Dichloro-benzoylamino)phenyl]-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 1)

Step a: Synthesis of *benzaldehyde oxime*

Sodium acetate (23.2 g) and hydroxylamine hydrochloride (19.6 g) was added to a solution of benzaldehyde (10 g) in ethanol (30 mL) at room temperature. The reaction mixture was stirred at room temperature for 2-3 hours. Solvent was evaporated under reduced pressure and the reaction mixture was taken into water and then extracted with ethyl acetate. The organic extracts were combined and washed with water and brine and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure to furnish the title compound (12.8 g).

Step b: Synthesis of *5-Methyl-3-phenyl-4,5-dihydro-isoxazole-4-carboxylic acid methyl ester.*

Methyl methacrylate (75 mL) and sodium hypochlorite (5 % aqueous solution) (250 mL) were added dropwise to a solution of benzaldehyde oxime obtained from *step a* (12.78 g) in tetrahydrofuran (25 mL). The reaction mixture was stirred for 50 hours at room temperature. The reaction mixture was concentrated, residue dissolved in water and then extracted with ethyl acetate. The organic extracts were washed with brine and dried over anhydrous sodium sulphate and concentrated to form crude product, which was then purified by column chromatography using 40 % ethyl acetate-hexane as eluent to furnish the title compound (13.2 g).

^{1}H NMR($CDCl_3$, 300 MHz):δ 7.66 (2H, d, 9Hz), 7.42-7.28 (3H, m), 3.81 (3H, s), 3.55 (2H, ABq, $\Delta\nu/J$=11.16, J=18Hz), 1.72 (3H, s); LCMS(m/e): 242.25 (M^++ Na)

Step c: Synthesis of *5-Methyl-3-phenyl-4,5-dihydro-isoxazole-4-carboxylic acid.*

Lithium hydroxide monohydrate (502 mg) was added to a solution of the compound (2.38 g) obtained from *step b* in tetrahydrofuran:methanol:water (3:1:1,10 mL) and stirred at room temperature for 2 hours. The reaction mixture was concentrated, dissolved in water and extracted with ethyl acetate. The aqueous layer was acidified using aqueous sodium hydrogen sulphate and extracted with ethyl acetate. The organic extracts were washed with water and brine and dried over anhydrous sodium sulphate and concentrated to furnish the title compound (1.7 g).

^{1}H NMR (DMSO, 300 MHz):δ 7.66 (2H, d, 6Hz), 7.45 (3H, m), 3.58 (2H, ABq, ΔV/J=7, J=18Hz), 1.56 (3H, s); LCMS: m/e : 228 (M^++ Na).

Step d: Synthesis of *(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid-methyl ester.*

2-amino-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid methyl ester was added to a solution of the compound (200 mg) obtained from *step c* in dimethylformamide (5 mL) and the reaction mixture stirred for 5 minutes at 0 °C. N-methylmorpholine (0.27 mL) and 1-hydroxbenzotriazole (0.14 g) were added to the reaction mixture and stirred for 30 minutes. 1-(3-dimethyl amino propyl)-3-ethyl carbodiimide (0.2 g) was added and stirred overnight at room temperature. The reaction mixture was quenched with water and then extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over anhydrous sodium sulphate and concentrated to form the crude residue, which was purified by column chromatography using 40 % ethyl acetate – hexane as eluent to furnish the title compound (210 mg).

^{1}H NMR ($CDCl_3$, 300 MHz):δ 7.63-7.56 (3H, m), 7.40-7.25 (10H, m), 7.00 (1H,m), 4.80 (1H, m), 3.81 (s) and 3.71 (s) [3H], 3.55 (1H, 1/2ABq, J=18Hz), 3.24-3.09 (3H, m), 1.649 (s) and 1.55(s) [3H]; LCMS (m/e): 554 (M^++1).

Step e: Synthesis of *(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid*

Lithium hydroxide monohydrate (16 mg) was added to a solution of the compound (210 mg) obtained from *step d* in tetrahydrofuran:methanol:water (3:1:1, 5 mL), and stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness, then dissolved in water and extracted with ethyl acetate. The aqueous layer was

acidified using aqueous sodium hydrogen sulphate solution and extracted with ethyl acetate. The organic extracts were washed with water and brine and dried over anhydrous sodium sulphate and concentrated to furnish the title compound (158 mg).

^{1}H NMR (DMSO, 300 MHz):δ 10.62 (1H, s), 7.96 (1H, m), 7.68-7.39 (11H, m), 7.42 (1H, d, 9Hz), 7.05 (1H, d, 9Hz), 4.44 (1H, bs), 3.63-3.41 (2H, m), 3.14-3.02 (2H, m), 1.99 (3H, s) & 1.45 (3H, s); LCMS(m/e): 540 (M^++1).

Analogues of (S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 1) described below can be prepared using the appropriate corresponding aldehyde in place of benzaldehyde, and appropriate corresponding propionic acid methylester in place of 2-amino-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid methyl ester (prepared as described in *Bioorg. Med. Chem.*, 10 (2002) 2051-2066 or *Bioorg. Med. Chem. Let.*, 12 (2002) 1591-1594).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 2); LCMS(m/e): 527 (M^++1);

(S)-3-(2',6'-Dimethoxy-biphenyl-4-yl)-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 3); LCMS(m/e): 489(M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-phenethyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 4); LCMS(m/e); 568(M^++1);

(S)-2-{[3-(3-Chloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 5); LCMS(m/e): 576 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2-fluoro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 6); LCMS(m/e): 558 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2,6-dimethoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 7); LCMS(m/e): 600 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino}-propionic acid. (Compound No. 8); LCMS(m/e): 570 (M^++1);

(S)-2-{[3-(2-Chloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 9); LCMS(m/e): 576 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2,6-dichloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 10); LCMS(m/e): 608 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[5-methyl-3-(1-phenyl-ethyl)-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid. (Compound No. 11); LCMS(m/e): 568.39 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 12); LCMS(m/e): 526 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(3,4-dimethoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino]-propionic acid (Compound No. 13); LCMS(m/e): 600 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-p-tolyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 14); LCMS(m/e): 554 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[(3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 15); LCMS(m/e): 513 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-quinolin-8-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 16); LCMS(m/e): 591 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-thiophen-2-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 17); LCMS(m/e): 546 (M^++1);

(S)-[(5-Methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-phenyl-acetic acid. (Compound No. 18); LCMS(m/e): 339 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[((5S)-5-methyl-3-quinolin-5-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid. (Compound No. 19); LCMS(m/e): 591 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[((5R)-5-methyl-3-quinolin-5-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid. (Compound No. 20); LCMS(m/e): 591 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[((5S)-5-methyl-3-pyridin-3-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid. (Compound No. 21); LCMS (m/e): 541 (M^++1);

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[((5R)-5-methyl-3-pyridin-3-yl-4,5-dihydro-isoxazle-5-carbonyl)-amino]-propionic acid. (Compound No. 22); LCMS (m/e): 541 (M^++1);

Example 2 - Scheme II and IV: Synthesis of (S)-2-[(3-Cyclohexyl-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 23)

Step a: Synthesis of cyclohexanecarbaldehyde oxime

Hydroxylamine hydrochloride (9.3 g) followed by sodium acetate (11 g) was added to a solution of cyclohexanecarboxaldehyde (5 g) dissolved in ethanol (15 mL) at room temperature. The reaction mixture was stirred for 2 hours at room temperature and concentrated, taken into water and extracted with ethyl acetate. The organic extracts were washed with water and brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to furnish the title compound (6.2 g).

Step b: Synthesis of cyclohexylhydroxamoyl *chloride*

N-chlorosuccinimide (1.96 g) in dimethylformamide was added dropwise over a period of 10 minutes to a solution of a compound (1.7 g) obtained from *step a* was dissolved in dimethylformamide (5 mL). The reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was poured into water, extracted with ethyl acetate. The combined organic extracts were washed with water and brine and dried over

anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to furnish the title compound as yellow oil (1.43 g).

Step c: Synthesis of *3-cyclohexyl-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester.*

Triethylamine (1.16 g) in tetrahydrofuran (5 mL) was added dropwise over a period of 10 minutes to a solution of the compound (1.43 g) obtained from *step b* dissolved in dry tetrahydrofuran (15 mL). The reaction mixture was stirred for 10 minutes and methyl methacrylate (1.61 mL) dissolved in tetrahydrofuran (3 mL) was added over a period of 15-20 minutes. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into water, extracted with ethyl acetate and washed with water and brine and dried over anhydrous sodium sulphate. Evaporation of the solvent furnished the title compound as yellow oil (1.38 g).

^{1}H NMR($CDCl_3$, 300 MHz):δ 3.78 (3H, s), 3.10 (2H, ABq, $\Delta\nu/J$=13.2, J=15Hz), 2.40 (1H, m), 1.91-1.89 (3H, m), 177-1.60 (10H, m); LCMS(m/e): 225 (M^++Na).

Step d: Synthesis of *3-cyclohexyl-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid.*

To a solution of the compound (1.38 g) obtained in *step c*; the general conditions as described in *step c* of Example 1 were followed using lithium hydroxide monohydrate (285 mg) in tetrahydrfuran:methanol:water (3:1:1, 5 mL) to furnish the title compound as a sticky yellow mass (510 mg).

^{1}H NMR ($CDCl_3$, 300 MHz):δ 3.15 (2H, ABq, $\Delta\nu/J$=9Hz, J=18Hz), 2.36 (1H, m), 1.95-1.57 (8H, m), 1.48 -1.25 (5H, m); LCMS (m/e): 211 (M^++1).

Step e: Synthesis of *(S)-2-[(3-Cyclohexyl-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid-methyl ester.*

To a solution of the compound (90 mg) in dimethylformamide (5 mL) obtained from *step d*, the general conditions as described in *step d* of Example 1 were followed using 2-amino-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid methyl ester (200 mg), N-methyl morpholine (108 mg) and 1-hydroxybenzotriazole (63.5 mg) and 1-(3-dimethyl amino propyl)-3-ethyl carbodiimide (90 mg) to furnish the title compound as yellow oil (180 mg).

^{1}H NMR ($CDCl_3$, 300 MHz):δ 7.59-7.54 (2H, m), 7.42-7.26 (5H, m), 7.16-7.10 (2H, m), 4.75-4.81 (1H, m), 3.75 (3H, s), 3.26-3.01 (3H, m), 3.00 (2H, ABq, $\Delta\nu$/J=7Hz, J=18Hz), 1.78-1.66 (4H, m), 1.57 (3H, s), 1.32-1.00 (6H, m); LCMS (m/e): 560 (M^++1).

Step f: Synthesis of *(S)-2-[(3-Cyclohexyl-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid*

To a solution of the compound (120 mg) obtained from *step e*, the general conditions as described in *step e* of Example 1 were followed using lithium hydroxide monohydrate (9.9 mg) in tetrahydrofuran:methanol:water (3:1:1, 5 mL) to furnish the title compound as (85 mg) yellow oil.

^{1}H NMR (DMSO, 300 MHz):δ 10.65 (1H, s), 7.81 (1H, d, 9Hz), 7.58-7.46 (6H, m), 7.18-7.09 (2H, m), 4.45 (1H, m), 3.06 (3H, m), 2.85(1H, 1\2 ABq, J=18Hz) 1.46 (3H, s), 1.44-1.24 (6H, m); LCMS (m/e) 546 (M^++1).

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-naphthalen-2-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid. (Compound No. 24); LCMS(m/e) 590 (M^++1);

(S)-2-[(3-tert-Butyl-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 25); LCMS (m/e) 520 (M^++1).

Example 3 - Scheme III and IV: Synthesis of (S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(3,5-dimethyl-4,5-dihydro-isoxazole-5-carbonyl}-amino]-propionic acid (Compound No. 26)

Step a: Synthesis of *3,5-Dimethyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester.*

Methyl methacrylate (10 g) and triethylamine (10 g) were added to a solution of nitroethane (5 g) in benzene – acetonitrile (70 mL – 30 mL). Trimethylsilyl chloride (10.8 g) was added slowly and the reaction mixture was refluxed for 2 hours. The reaction mixture was filtered and the filtrate was refluxed with *p*-toluenesuphonic acid for 2 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic extract was washed with water and brine and dried over anhydrous sodium sulphate and concentrated to furnish the title compound as yellow oil (4.2 g).

Step b: Synthesis of *3,5-Dimethyl-4,5-dihydro-isoxazle-5-carboxylic acid.*

To a solution of a compound (500 mg) obtained from *Step a*, the general conditions as described in *step c* of Example 1 was followed using lithium hydroxide monohydrate (133 mg) in tetrahydrofuran:methanol:water (3:1:1, 3 mL) to furnish the title compound as light yellow solid (370 mg).

^{1}H NMR (DMSO-d_6, 300 MHz):δ 3.1 (2H, ABq, Δ^Y/J=7.33Hz, J=18Hz), 1.90 (3H, s) 1.47 (3H, s).

Step c: Synthesis of *4-Methyl-3-phenyl-4,5-dihydro-isoxazole-4-carboxylic acid methyl ester.*

To a solution of compound (76 mg) obtained from *step b*, the general conditions as described in *step d* of Example 1 were followed using N-methyl morpholine (108 mg) 1-hydroxy benzotriazole (162 mg) and 1-(3-dimethyl amino propyl)-3-ethyl carbodiimide (102 mg) in dimethylformamide (3 mL) to furnish the title compound (225 mg).

^{1}H NMR ($CDCl_3$, 300 MHz):δ 7.54-7.79 (2H, m), 7.26-7.39 (5H, m), 7.11-7.16 (2H, m), 4.77-4.86 (1H, m), 3.74(s) and 3.76(s) [3H], 2.74-3.34 (4H, m), 1.95 (3H, s), 1.48-1.53 (3H, bs); LCMS (m/e): 492.35 (M^++1).

Step d: Synthesis of *(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(3,5-dimethyl-4,5-dihydro-isoxazole-5-carbonyl}-amino]-propionic acid*

To a solution of compound (225 mg) obtained from *step c,* the general conditions as described in *step e* of Example 1 were followed using lithium hydroxide monohydrate (10 mg) in tetrahydrofuran:methanol:water (3:1:1, 5 mL) to furnish the title compound as an off-white solid (180 mg).

^{1}H NMR (DMSO, 300 MHz):δ10.66 (1H,s), 7.82 (1H,d,6Hz), 7.59-7.46 (5H,m), 7.17-7.09 (2H,m), 4.45 (1H,d, J=6Hz,), 3.18-2.88 (4H,m), 1.91 (3H,s), 1.41(s) and 1.32 (s) [3H].

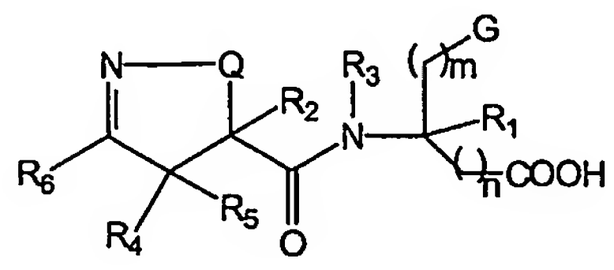
Primary Screening- Cell Adhesion Assay

VCAM-1 (100 ng/well) was coated in Maxisorp microtitre modules at 4 °C overnight. Non-specific blocking was carried out with 3 % BSA for two hours and the wells washed with TBS (50 mM) Tris, 0.15M NaCl pH 7.4, 0.1 mM $CaCl_2$, 0.1 mM $MgCl_2$). U937 cells were suspended in fresh medium and incubated at 37 °C for two hours

before the assay. Cells were then washed in TBS solution and 180 µl of cell suspension ($1x10^6$ cells/mL in TBS buffer) was added per well in VCAM-1 coated wells. 20 µL of sample solution in 50 % DMSO and 50 % TBS was then added and the cells are incubated at 37 °C for one hour three to five dilutions of each sample were tested in duplicate in a primary screen, samples are tested at 1, 10 and 100 µm. If activity was present, the compounds were tested at lower (<1 µm) concentrations. After incubation, the non-adherent cells were removed by washing with TBS and the numbers of adhered cells are quantified by LDH activity estimation. The percent adhesion was calculated as compared to control. Compounds provided herein showed activities in the range of nM-100 µM following this assay. For example, compounds tested showed activities of between about 100 μM to about 0.004 μM, for example, between about 10 μM and about 0.004 μM, or between about 2.7 μM and about 0.004 μM, or between about 0.30 μM and about 0.004 μM.

We claim

1. A compound having a structure of Formula I:



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides, wherein

m and **n** are integers with the values 0, 1 or 2;

Q is O or S;

$\mathbf{R_1}$ is hydrogen or methyl;

$\mathbf{R_2}$ is hydrogen or $(CH_2)_f(O)_gR_k$, wherein

f is 0-6, g is 0-1, and R_k is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or aryl;

$\mathbf{R_4}$ and $\mathbf{R_5}$ are each independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, heteroaryl, heterocyclyl, C_1-C_4 heteroarylalkyl and C_1-C_4 heterocyclylalkyl;

$\mathbf{R_6}$ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl; and

$\mathbf{R_3}$ is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, C_1-C_4 heteroarylalkyl or C_1-C_4 heterocyclylalkyl, and **G** is aryl optionally substituted with one or more of X, $\equiv\!\!-(CH_2)_q-X$, heteroaryl substituted with one or more X or heterocyclyl substituted with one or more X; or when G is aryl, $\mathbf{R_3}$ and **G** together optionally form a benzofused heterocyclic 5-6 membered ring along with the N to which R_3 is attached, wherein

q is an integer 0-1 with the proviso that q cannot be 0 when X is a derivative of heteroatom, and

X is hydrogen, alkyl, alkenyl, alkynyl, halogen, acyl, CF_3, nitro, carboxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, $COOR_9$,-$(CH_2)_{0-4}$-O-R′, –C(=O)NR_7R_8, $(CH_2)_{0-4}NR_7R_8$, $NHYR_9$ or -$NR_jC(=T)NR_dR_c$,

wherein

Y is -C(=O), -C(=S) or SO_2;

R_d is OH or R_c;

T is O, S, -N(CN), -$N(NO_2)$ or -$CH(NO_2)$;

R_9 is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

R′ is hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryl, acyl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl or $C(=O)NR_tR_c$;

R_7 and R_8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl, or R_7 and R_8 together join to form a 5-8 membered-ring containing 0-4 heteroatoms selected from O, S and N, wherein the ring is optionally benzofused and optionally substituted with one or more of alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, carboxy, alkoxy, aryloxy, acyl, aryl, amino, substituted amino, oxo, CF_3, halogen, cycloalkylalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or $OC(=O)NR_tR_c$;

R_t and R_c are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or SO_2R_9; and

R_j is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, C_1-C_6 aralkyl, C_1-C_6 heteroarylalkyl or C_1-C_6 heterocyclylalkyl, wherein

R_j and R_c are optionally together a part of a 5- or 6-membered ring along with the N atom to which they are attached,

with the provisos that:

a) when n is 1 and Q is O, then R_6 cannot be substituted with amino, substituted amino, $Z(CH_2)_pR_w$ or ZR_v,

wherein Z is O or $S(O)_q$, q and p is an integer 0-2, R_w is amino, substituted amino and R_v is cycloalkyl, cycloalkylalkyl, heterocyclyl or heterocyclylalkyl;

b) when Q is O, then R_6 cannot be a 5-membered N-containing heteroaryl having one or more heteroatoms selected from S, O or N, or C=O or SO_2 group in the ring; or

R_6 cannot be a 5-membered N containing heteroaryl having substituted or unsubstituted amino groups; and one or more of S, O, N, C=O or SO_2 in the heteroaryl ring; and

c) when Q is O, then R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring; or

R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring and substituted or unsubstituted amino groups, and the point of attachment of the heteroaryl is from the carbon atom adjacent to N atom.

2. The compound of claim 1 wherein Q is O.

3. The compound of claim 1, wherein R_6 is alkyl, aryl, cycloalkyl, aralkyl, heterocyclyl or heteroaryl.

4. The compound of claim 1, wherein R_6 is optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl.

5. The compound of claim 1, wherein R_6 is phenyl, chlorophenyl, fluorophenyl, dichlorophenyl, methoxyphenyl, dimethoxyphenyl, tolyl, tert-butyl, methylphenylethyl, cyclohexyl, thiophenyl, pyridinyl, quinolinyl or naphthalenyl.

6. The compound of claim 1, wherein R_4 and R_5 are each hydrogen.

7. The compound of claim 1, wherein R_3 is alkyl or hydrogen.

8. The compound of claim 1, wherein R_2 is an alkyl or hydrogen.

9. The compound of claim 1, wherein R_2 is methyl.

10. The compound of claim 1, wherein R_1 is hydrogen.

11. The compound of claim 1, wherein G is optionally substituted aryl.

12. The compound of claim 1, wherein G is phenyl, dichloro-benzoylamino-phenyl, dichloro-benzyloxyphenyl or dimethoxybiphenyl.

13. A compound selected from:

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 1),

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 2),

(S)-3-(2′,6′-Dimethoxy-biphenyl-4-yl)-2-[(5-methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 3),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-phenethyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 4),

(S)-2-{[3-(3-Chloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 5),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2-fluoro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 6),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2,6-dimethoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 7),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino}-propionic acid (Compound No. 8),

(S)-2-{[3-(2-Chloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 9),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(2,6-dichloro-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 10),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[5-methyl-3-(1-phenyl-ethyl)-4,5-dihydro-isoxazole-5-carbonyl]-amino}-propionic acid (Compound No. 11),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 12),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[3-(3,4-dimethoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-amino]-propionic acid (Compound No. 13),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-p-tolyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 14),

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[(3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 15),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-quinolin-8-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 16),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-thiophen-2-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 17),

(S)-[(5-Methyl-3-phenyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-phenyl-acetic acid (Compound No. 18),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-quinolin-5-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 19),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-quinolin-5-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 20),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-pyridin-3-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 21),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-pyridin-3-yl-4,5-dihydro-isoxazle-5-carbonyl)-amino]-propionic acid (Compound No. 22),

(S)-2-[(3-Cyclohexyl-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 23),

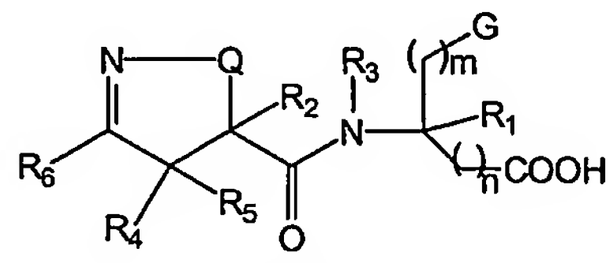
(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(5-methyl-3-naphthalen-2-yl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-propionic acid (Compound No. 24),

(S)-2-[(3-tert-Butyl-5-methyl-4,5-dihydro-isoxazole-5-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 25),

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[(3,5-dimethyl-4,5-dihydro-isoxazole-5-carbonyl}-amino]-propionic acid (Compound No. 26), and

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, N-oxides or polymorphs.

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound having a structure of Formula I:



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides, wherein

m and **n** are integers with the values 0, 1 or 2;

Q is O or S;

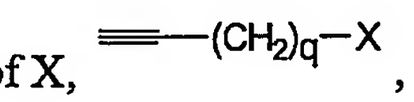
$\mathbf{R_1}$ is hydrogen or methyl;

$\mathbf{R_2}$ is hydrogen or $(CH_2)_f(O)_gR_k$, wherein

f is 0-6, g is 0-1, and R_k is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or aryl;

$\mathbf{R_4}$ and $\mathbf{R_5}$ are each independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, heteroaryl, heterocyclyl, C_1-C_4 heteroarylalkyl and C_1-C_4 heterocyclylalkyl;

$\mathbf{R_6}$ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl; and

$\mathbf{R_3}$ is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, C_1-C_4 heteroarylalkyl or C_1-C_4 heterocyclylalkyl, and **G** is aryl optionally substituted with one or more of X,  , heteroaryl substituted with one or more X or heterocyclyl substituted with one or more X; or when G is aryl, $\mathbf{R_3}$ and **G** together optionally form a benzofused heterocyclic 5-6 membered ring along with the N to which R_3 is attached, wherein

q is an integer 0-1 with the proviso that q cannot be 0 when X is a derivative of heteroatom, and

X is hydrogen, alkyl, alkenyl, alkynyl, halogen, acyl, CF_3, nitro, carboxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, $COOR_9$,-$(CH_2)_{0\text{-}4}$-O-R', –C(=O)NR_7R_8, $(CH_2)_{0\text{-}4}NR_7R_8$, $NHYR_9$ or -$NR_jC(=T)NR_dR_c$,

wherein

Y is -C(=O), -C(=S) or SO_2;

R_d is OH or R_c;

T is O, S, -N(CN), -$N(NO_2)$ or -$CH(NO_2)$;

R_9 is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

R′ is hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryl, acyl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl or $C(=O)NR_tR_c$;

R_7 and R_8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl, or R_7 and R_8 together join to form a 5-8 membered-ring containing 0-4 heteroatoms selected from O, S and N, wherein the ring is optionally benzofused and optionally substituted with one or more of alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, carboxy, alkoxy, aryloxy, acyl, aryl, amino, substituted amino, oxo, CF_3, halogen, cycloalkylalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or $OC(=O)NR_tR_c$;

R_t and R_c are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or SO_2R_9; and

R_j is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, C_1-C_6 aralkyl, C_1-C_6 heteroarylalkyl or C_1-C_6 heterocyclylalkyl, wherein

R_j and R_c are optionally together a part of a 5- or 6-membered ring along with the N atom to which they are attached,

with the provisos that:

a) when n is 1 and Q is O, then R_6 cannot be substituted with amino, substituted amino, $Z(CH_2)_pR_w$ or ZR_v,

wherein Z is O or $S(O)_q$, q and p is an integer 0-2, R_w is amino, substituted amino and R_v is cycloalkyl, cycloalkylalkyl, heterocyclyl or heterocyclylalkyl;

b) when Q is O, then R_6 cannot be a 5-membered N-containing heteroaryl having one or more heteroatoms selected from S, O or N, or C=O or SO_2 group in the ring; or

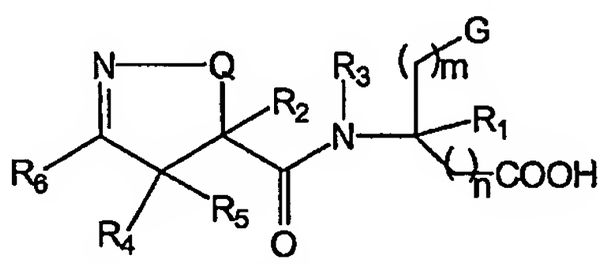
R_6 cannot be a 5-membered N containing heteroaryl having substituted or unsubstituted amino groups; and one or more of S, O, N, C=O or SO_2 in the heteroaryl ring; and

c) when Q is O, then R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring; or

R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring and substituted or unsubstituted amino groups, and the point of attachment of the heteroaryl is from the carbon atom adjacent to N atom;

together with one or more pharmaceutically acceptable carriers, excipients or diluents.

15. A method of treating an animal or a human suffering from bronchial asthma, rheumatoid arthritis, type I diabetes, multiple sclerosis, psoriasis, allograft rejection or other inflammation and/or autoimmune disorders comprising administering to said animal or human a therapeutically effective amount of a compound having a structure of Formula I:



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides, wherein

m and **n** are integers with the values 0, 1 or 2;

Q is O or S;

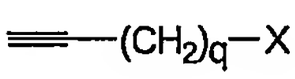
R_1 is hydrogen or methyl;

R_2 is hydrogen or $(CH_2)_f(O)_gR_k$, wherein

f is 0-6, g is 0-1, and R_k is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or aryl;

$\mathbf{R_4}$ and $\mathbf{R_5}$ are each independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, heteroaryl, heterocyclyl, C_1-C_4 heteroarylalkyl and C_1-C_4 heterocyclylalkyl;

$\mathbf{R_6}$ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl; and

$\mathbf{R_3}$ is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, C_1-C_4 heteroarylalkyl or C_1-C_4 heterocyclylalkyl, and **G** is aryl optionally substituted with one or more of X,  , heteroaryl substituted with one or more X or heterocyclyl substituted with one or more X; or when G is aryl, $\mathbf{R_3}$ and **G** together optionally form a benzofused heterocyclic 5-6 membered ring along with the N to which R_3 is attached, wherein

q is an integer 0-1 with the proviso that q cannot be 0 when X is a derivative of heteroatom, and

X is hydrogen, alkyl, alkenyl, alkynyl, halogen, acyl, CF_3, nitro, carboxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, $COOR_9$,-$(CH_2)_{0\text{-}4}$-O-R′, –C(=O)NR_7R_8, $(CH_2)_{0\text{-}4}NR_7R_8$, $NHYR_9$ or -$NR_jC(=T)NR_dR_c$,

wherein

Y is -C(=O), -C(=S) or SO_2;

R_d is OH or R_c;

T is O, S, -N(CN), -$N(NO_2)$ or -$CH(NO_2)$;

R_9 is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

R′ is hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryl, acyl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl or $C(=O)NR_tR_c$;

R_7 and R_8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, or

heterocyclylalkyl, or R_7 and R_8 together join to form a 5-8 membered-ring containing 0-4 heteroatoms selected from O, S and N, wherein the ring is optionally benzofused and optionally substituted with one or more of alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, carboxy, alkoxy, aryloxy, acyl, aryl, amino, substituted amino, oxo, CF_3, halogen, cycloalkylalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or $OC(=O)NR_tR_c$;

R_t and R_c are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or SO_2R_9; and

R_j is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, C_1-C_6 aralkyl, C_1-C_6 heteroarylalkyl or C_1-C_6 heterocyclylalkyl, wherein

R_j and R_c are optionally together a part of a 5- or 6-membered ring along with the N atom to which they are attached,

with the provisos that:

a) when n is 1 and Q is O, then R_6 cannot be substituted with amino, substituted amino, $Z(CH_2)_pR_w$ or ZR_v,

wherein Z is O or $S(O)_q$, q and p is an integer 0-2, R_w is amino, substituted amino and R_v is cycloalkyl, cycloalkylalkyl, heterocyclyl or heterocyclylalkyl;

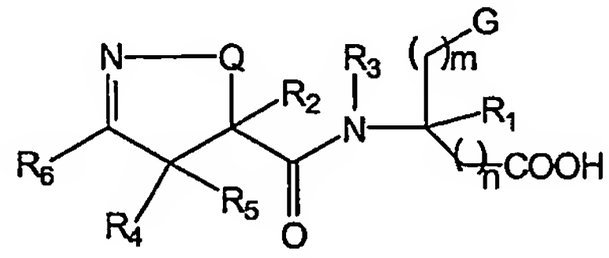
b) when Q is O, then R_6 cannot be a 5-membered N-containing heteroaryl having one or more heteroatoms selected from S, O or N, or C=O or SO_2 group in the ring; or

R_6 cannot be a 5-membered N containing heteroaryl having substituted or unsubstituted amino groups; and one or more of S, O, N, C=O or SO_2 in the heteroaryl ring; and

c) when Q is O, then R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring; or

R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring and substituted or unsubstituted amino groups, and the point of attachment of the heteroaryl is from the carbon atom adjacent to N atom.

16. A method of preventing, inhibiting or suppressing cell adhesion in an animal or human comprising administering to said animal or human a therapeutically effective amount of a compound having a structure of Formula I:



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides, wherein

m and **n** are integers with the values 0, 1 or 2;

Q is O or S;

R_1 is hydrogen or methyl;

R_2 is hydrogen or $(CH_2)_f(O)_gR_k$, wherein

f is 0-6, g is 0-1, and R_k is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or aryl;

R_4 and **R_5** are each independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, heteroaryl, heterocyclyl, C_1-C_4 heteroarylalkyl and C_1-C_4 heterocyclylalkyl;

R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl; and

R_3 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, C_1-C_4 heteroarylalkyl or C_1-C_4 heterocyclylalkyl, and **G** is aryl optionally substituted with one or more of X, $\equiv\!\!-(CH_2)_q-X$,

heteroaryl substituted with one or more X or heterocyclyl substituted with one or more X; or when G is aryl, R_3 and G together optionally form a benzofused heterocyclic 5-6 membered ring along with the N to which R_3 is attached, wherein

q is an integer 0-1 with the proviso that q cannot be 0 when X is a derivative of heteroatom, and

X is hydrogen, alkyl, alkenyl, alkynyl, halogen, acyl, CF_3, nitro, carboxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, $COOR_9$, $-(CH_2)_{0-4}-O-R'$, $-C(=O)NR_7R_8$, $(CH_2)_{0-4}NR_7R_8$, $NHYR_9$ or $-NR_jC(=T)NR_dR_c$,

wherein

Y is -C(=O), -C(=S) or SO_2;

R_d is OH or R_c;

T is O, S, -N(CN), $-N(NO_2)$ or $-CH(NO_2)$;

R_9 is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

R′ is hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryl, acyl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl or $C(=O)NR_tR_c$;

R_7 and R_8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl, or R_7 and R_8 together join to form a 5-8 membered-ring containing 0-4 heteroatoms selected from O, S and N, wherein the ring is optionally benzofused and optionally substituted with one or more of alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, carboxy, alkoxy, aryloxy, acyl, aryl, amino, substituted amino, oxo, CF_3, halogen, cycloalkylalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or $OC(=O)NR_tR_c$;

R_t and R_c are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or SO_2R_9; and

R_j is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, C_1-C_6 aralkyl, C_1-C_6 heteroarylalkyl or C_1-C_6 heterocyclylalkyl, wherein

R_j and R_c are optionally together a part of a 5- or 6-membered ring along with the N atom to which they are attached,

with the provisos that:

a) when n is 1 and Q is O, then R_6 cannot be substituted with amino, substituted amino, $Z(CH_2)_pR_w$ or ZR_v,

wherein Z is O or $S(O)_q$, q and p is an integer 0-2, R_w is amino, substituted amino and R_v is cycloalkyl, cycloalkylalkyl, heterocyclyl or heterocyclylalkyl;

b) when Q is O, then R_6 cannot be a 5-membered N-containing heteroaryl having one or more heteroatoms selected from S, O or N, or C=O or SO_2 group in the ring; or

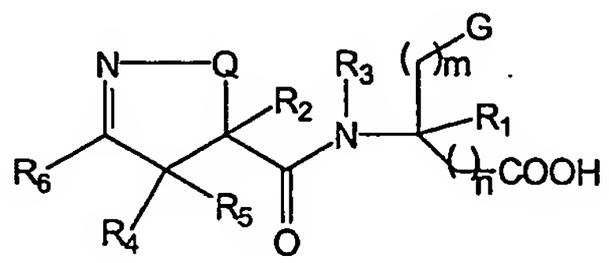
R_6 cannot be a 5-membered N containing heteroaryl having substituted or unsubstituted amino groups; and one or more of S, O, N, C=O or SO_2 in the heteroaryl ring; and

c) when Q is O, then R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring; or

R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring and substituted or unsubstituted amino groups, and the point of attachment of the heteroaryl is from the carbon atom adjacent to N atom.

17. A method of treating an animal or a human suffering from bronchial asthma, rheumatoid arthritis, type I diabetes, multiple sclerosis, psoriasis, allograft rejection or other inflammation and/or autoimmune disorders comprising administering to said animal or human a therapeutically effective amount of the pharmaceutical composition

comprising a therapeutically effective amount of a compound having a structure of Formula I:



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides, wherein

m and **n** are integers with the values 0, 1 or 2;

Q is O or S;

$\mathbf{R_1}$ is hydrogen or methyl;

$\mathbf{R_2}$ is hydrogen or $(CH_2)_f(O)_gR_k$, wherein

f is 0-6, g is 0-1, and R_k is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or aryl;

$\mathbf{R_4}$ and $\mathbf{R_5}$ are each independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, heteroaryl, heterocyclyl, C_1-C_4 heteroarylalkyl and C_1-C_4 heterocyclylalkyl;

$\mathbf{R_6}$ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl; and

$\mathbf{R_3}$ is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, C_1-C_4 heteroarylalkyl or C_1-C_4 heterocyclylalkyl, and **G** is aryl optionally substituted with one or more of X, $\equiv\!\!-(CH_2)_q-X$,

heteroaryl substituted with one or more X or heterocyclyl substituted with one or more X; or when G is aryl, $\mathbf{R_3}$ and **G** together optionally form a benzofused heterocyclic 5-6 membered ring along with the N to which R_3 is attached, wherein

q is an integer 0-1 with the proviso that q cannot be 0 when X is a derivative of heteroatom, and

X is hydrogen, alkyl, alkenyl, alkynyl, halogen, acyl, CF_3, nitro, carboxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, $COOR_9$,-$(CH_2)_{0-4}$-O-R′, –C(=O)NR_7R_8, $(CH_2)_{0-4}NR_7R_8$, $NHYR_9$ or -$NR_jC(=T)NR_dR_c$,

wherein

Y is -C(=O), -C(=S) or SO_2;

R_d is OH or R_c;

T is O, S, -N(CN), -$N(NO_2)$ or -$CH(NO_2)$;

R_9 is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

R′ is hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryl, acyl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl or $C(=O)NR_tR_c$;

R_7 and R_8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl, or R_7 and R_8 together join to form a 5-8 membered-ring containing 0-4 heteroatoms selected from O, S and N, wherein the ring is optionally benzofused and optionally substituted with one or more of alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, carboxy, alkoxy, aryloxy, acyl, aryl, amino, substituted amino, oxo, CF_3, halogen, cycloalkylalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or $OC(=O)NR_tR_c$;

R_t and R_c are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or SO_2R_9; and

R_j is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, C_1-C_6 aralkyl, C_1-C_6 heteroarylalkyl or C_1-C_6 heterocyclylalkyl, wherein

R_j and R_c are optionally together a part of a 5- or 6-membered ring along with the N atom to which they are attached,

with the provisos that:

a) when n is 1 and Q is O, then R_6 cannot be substituted with amino, substituted amino, $Z(CH_2)_pR_w$ or ZR_v,

wherein Z is O or $S(O)_q$, q and p is an integer 0-2, R_w is amino, substituted amino and R_v is cycloalkyl, cycloalkylalkyl, heterocyclyl or heterocyclylalkyl;

b) when Q is O, then R_6 cannot be a 5-membered N-containing heteroaryl having one or more heteroatoms selected from S, O or N, or C=O or SO_2 group in the ring; or

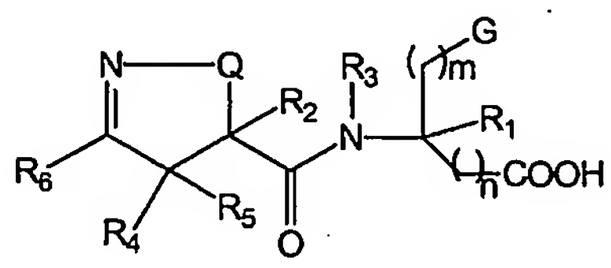
R_6 cannot be a 5-membered N containing heteroaryl having substituted or unsubstituted amino groups; and one or more of S, O, N, C=O or SO_2 in the heteroaryl ring; and

c) when Q is O, then R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring; or

R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring and substituted or unsubstituted amino groups, and the point of attachment of the heteroaryl is from the carbon atom adjacent to N atom;

together with one or more pharmaceutically acceptable carriers, excipients or diluents.

18. A method of preventing, inhibiting or suppressing cell adhesion in an animal or human comprising administering to said animal or human a therapeutically effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a compound having a structure of Formula I:



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides, wherein

m and **n** are integers with the values 0, 1 or 2;

Q is O or S;

$\mathbf{R_1}$ is hydrogen or methyl;

$\mathbf{R_2}$ is hydrogen or $(CH_2)_f(O)_gR_k$, wherein

f is 0-6, g is 0-1, and R_k is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or aryl;

$\mathbf{R_4}$ and $\mathbf{R_5}$ are each independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, heteroaryl, heterocyclyl, C_1-C_4 heteroarylalkyl and C_1-C_4 heterocyclylalkyl;

$\mathbf{R_6}$ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl; and

$\mathbf{R_3}$ is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, aryl, C_1-C_4 aralkyl, C_1-C_4 heteroarylalkyl or C_1-C_4 heterocyclylalkyl, and **G** is aryl optionally substituted with one or more of X, $\equiv\!\!-(CH_2)_q-X$, heteroaryl substituted with one or more X or heterocyclyl substituted with one or more X; or when G is aryl, $\mathbf{R_3}$ and **G** together optionally form a benzofused heterocyclic 5-6 membered ring along with the N to which R_3 is attached, wherein

q is an integer 0-1 with the proviso that q cannot be 0 when X is a derivative of heteroatom, and

X is hydrogen, alkyl, alkenyl, alkynyl, halogen, acyl, CF_3, nitro, carboxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, $COOR_9$,-$(CH_2)_{0-4}$-O-R′, –C(=O)NR_7R_8, $(CH_2)_{0-4}NR_7R_8$, $NHYR_9$ or -$NR_jC(=T)NR_dR_c$,

wherein

Y is -C(=O), -C(=S) or SO_2;

R_d is OH or R_c;

T is O, S, -N(CN), -N(NO_2) or -CH(NO_2);

R_9 is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

R′ is hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryl, acyl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl or $C(=O)NR_tR_c$;

R_7 and R_8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl, or R_7 and R_8 together join to form a 5-8 membered-ring containing 0-4 heteroatoms selected from O, S and N, wherein the ring is optionally benzofused and optionally substituted with one or more of alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, carboxy, alkoxy, aryloxy, acyl, aryl, amino, substituted amino, oxo, CF_3, halogen, cycloalkylalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or $OC(=O)NR_tR_c$;

R_t and R_c are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or SO_2R_9; and

R_j is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, C_1-C_6 aralkyl, C_1-C_6 heteroarylalkyl or C_1-C_6 heterocyclylalkyl, wherein

R_j and R_c are optionally together a part of a 5- or 6-membered ring along with the N atom to which they are attached,

with the provisos that:

a) when n is 1 and Q is O, then R_6 cannot be substituted with amino, substituted amino, $Z(CH_2)_pR_w$ or ZR_v,

wherein Z is O or $S(O)_q$, q and p is an integer 0-2, R_w is amino, substituted amino and R_v is cycloalkyl, cycloalkylalkyl, heterocyclyl or heterocyclylalkyl;

b) when Q is O, then R_6 cannot be a 5-membered N-containing heteroaryl having one or more heteroatoms selected from S, O or N, or C=O or SO_2 group in the ring; or

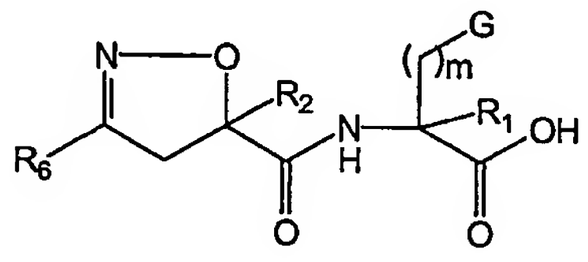
R_6 cannot be a 5-membered N containing heteroaryl having substituted or unsubstituted amino groups; and one or more of S, O, N, C=O or SO_2 in the heteroaryl ring; and

c) when Q is O, then R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring; or

R_6 cannot be 6-membered N-containing heteroaryl having one or more N-atom, C=O or C=NH in the ring and substituted or unsubstituted amino groups, and the point of attachment of the heteroaryl is from the carbon atom adjacent to N atom;

together with one or more pharmaceutically acceptable carriers, excipients or diluents.

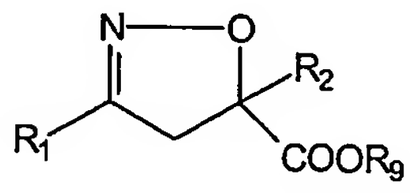
19. A process for preparing a compound of Formula IX



Formula IX

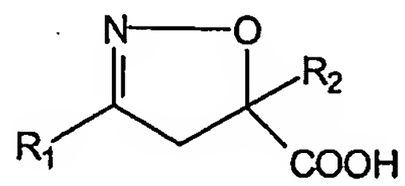
comprising the steps of:

a) hydrolyzing a compound of Formula V



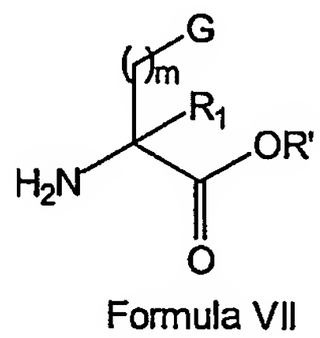
Formula V

to form a compound of Formula VI;



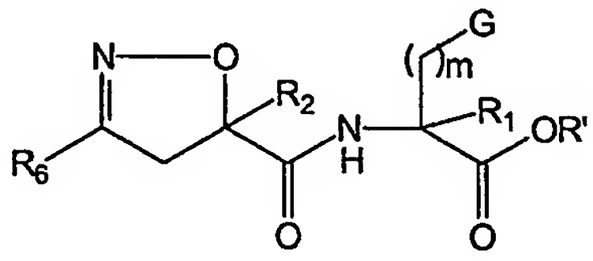
Formula VI

b) reacting the compound of Formula VI with a compound of Formula VII



Formula VII

to form a compound of Formula VIII; and



Formula VIII

c) hydrolyzing the compound of Formula VIII to yield a compound of Formula IX,

wherein

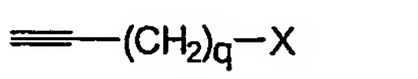
m is an integer with a value of 0, 1 or 2;

$\mathbf{R_1}$ is hydrogen or methyl;

$\mathbf{R_2}$ is hydrogen or $(CH_2)_f(O)_gR_k$, wherein

f is 0-6, g is 0-1, and R_k is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or aryl;

$\mathbf{R_6}$ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl; and

G is aryl optionally substituted with one or more of X,  ,

heteroaryl substituted with one or more X or heterocyclyl substituted with one or more X; or when G is aryl, wherein

q is an integer 0-1 with the proviso that q cannot be 0 when X is a derivative of heteroatom, and

X is hydrogen, alkyl, alkenyl, alkynyl, halogen, acyl, CF_3, nitro, carboxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, $COOR_9$,-$(CH_2)_{0-4}$-O-R′, –C(=O)NR_7R_8, $(CH_2)_{0-4}NR_7R_8$, $NHYR_9$ or -$NR_jC(=T)NR_dR_c$,

wherein

Y is -C(=O), -C(=S) or SO_2;

R_d is OH or R_c;

T is O, S, -N(CN), -N(NO_2) or -CH(NO_2);

R_9 is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

R′ is hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryl, acyl, heteroaryl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl or C(=O)NR_tR_c;

R_7 and R_8 are each independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl, or R_7 and R_8 together join to form a 5-8 membered-ring containing 0-4 heteroatoms selected from O, S and N, wherein the ring is optionally benzofused and optionally substituted with one or more of alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, carboxy, alkoxy, aryloxy, acyl, aryl, amino, substituted amino, oxo, CF_3, halogen, cycloalkylalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or OC(=O)NR_tR_c;

R_t and R_c are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or SO_2R_9; and

R_j is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, C_1-C_6 aralkyl, C_1-C_6 heteroarylalkyl or C_1-C_6 heterocyclylalkyl, wherein

R_j and R_c are optionally together a part of a 5- or 6-membered ring along with the N atom to which they are attached.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000348

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D261/04 C07D409/04 C07D401/04 A61K31/4155 A61P29/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/37492 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 28 November 1996 (1996-11-28) cited in the application the whole document	1-19
A	US 5 710 159 A (VOSS ET AL) 20 January 1998 (1998-01-20) cited in the application the whole document	1-19

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2006	06/06/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Nikolai, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000348

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PORTER J R ET AL: "Discovery and Evaluation of N-(triazin-1,3,5-yl) Phenylalanine Derivatives as VLA-4 Integrin Antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 12, no. 12, 2002, pages 1591-1594, XP002312994 ISSN: 0960-894X the whole document	1-19
X	QUAN M L ET AL: "Design and Synthesis of Isoxazoline Derivatives as Factor Xa Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 15, 1999, pages 2760-2773, XP002213660 ISSN: 0022-2623 the whole document	19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/000348

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 15 - 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2006/000348

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9637492 A	28-11-1996	AU 5876296 A	11-12-1996
		CA 2221980 A1	28-11-1996
		EP 0828737 A1	18-03-1998
		JP 11506436 T	08-06-1999
US 5710159 A	20-01-1998	NONE	